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METABOLISM

AND PRACTICAL MEDICINE

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METABOLISM

PHYSIOLOGY AND PATHOLOGY

WITH ITS APPLICATIONS TO PRACTICAL MEDICINE

BY

CARL VON NOORDEN

PROFESSOR OF THE FIRST UNIVERSITY MEDICAL CLINIC, VIENNA

VOL. II.—THE PATHOLOGY OF METABOLISM

BY

CARL VON NOORDEN, FR. KRAUS, AD. SCHMIDT, W. WEINTRAUD, M. MATTHES, AND H. STRAUSS

ANGLO-AMERICAN ISSUE UNDER THE EDITORSHIP OF

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CHICAGO

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1907

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LITERATURE

The following abbreviations are used throughout :

A. C.	Annali di Chimica.
A. c. p.	Annales de Chimie et de physique.
A. C.-Z.	Allgemeine medicinische Central-Zeitung.
A. D.	Arbeiten des pharmakologischen Inst. zu Dorpat.
A. D. S.	Annales de Dermatologie et de Syphilologie.
A. F.	Archivio di Farmacologia e Terapeutica.
A. F. s.	Archivio di Farmacologia sper.
A. H.	Archiv der Heilkunde.
A. i. B.	Archives italiennes de Biologie.
A. J. M. S.	American Journal of the Medical Sciences.
A. J. O.	American Journal of Obstetrics.
A. J. P.	American Journal of Physiology.
A. J. U.	American Journal of Urology.
A. K.	Arbeiten aus der städtischen Krankenh. zu Frankfurt-a-Main.
A. k. G.	Arbeiten aus dem kaiserl. Gesundheitsamte.
A. L. I.	Arbeiten aus dem Leipzig physiolog. Institut.
A. M.	Archives of Medicine (New York).
A. P.	Anat. physiol. Untersuchungen (Wien).
A. p. H.	Archiv für physiologische Heilkunde.
A. Ph.	Archivio di Pharmakoterap.
A. S. B. A. s. b.	Archives de Sciences biologiques, St. Petersb.
A. T. S.	Archiv für Tropen und Schiffshagg.
Ac. T.	Accademia medica di Torini.
An. c. F.	Annali di Chimica e di Farmacologia.
An. c. P.	Annalen der Chemie und Pharmacologie.
An. g.-u.	Annales des Maladies des organes génito-urinaires.
An. gy.	Annales de gynécologie.
An. hy.	Annales d'hygiène publique.
An. I.	Annali d'Igiene sperimentale.
An. m.-p.	Annales médico-psychologiques.
An. P.	Annales de l'Institut Pasteur.
An. S.	Annals of Surgery.
An. S. K.	Ann. Städt. Allg. Krankenh. (München).
An. T.	Annales de Thérap. dermat. et syphil.
An. u.	Annales univ. de Méd. et Chirurgie.
Ar. A. P.	Archiv für Anatomie und Physiologie.
Ar. B.	Boas's Archiv.
Ar. c. B.	Archives cliniques de Bordeaux.
Ar. D. S.	Archiv für Dermatologie und Syphil.
Ar. E. O.	Archiv für Entwickelungsmech. der Organismen.

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Ar. F.	Archivio di Fisiologia.
Ar. g. m.	Archives générales de Médecine.
Ar. Gy.	Archiv für Gynäkologie.
Ar. H.	Archiv für Heilkunde.
Ar. h. B.	Archiv für die holländischen Beitr. z. Natur.- und Heilkunde.
Ar. Hy.	Archiv für Hygiene.
Ar. i. B.	Archives italiennes de Biologie.
Ar. i. M.	Archivio italiano di Clinica Medica.
Ar. i. P.	Archives internat. de Pharmac. et de Thérap.
Ar. K.	Archiv für Kinderheilkunde.
Ar. k. C.	Archiv für klinische Chirurgie (Langenbeck's).
Ar. M.	Archiv für klinische Medicin.
Ar. m. A.	Archiv für mikroscop. Anatomie.
Ar. m. ex.	Archives de médecine expérimentale.
Ar. n.	Archives de Névrologie.
Ar. p. A.	Archiv für patholog. Anat. und Physiol. (Virchow).
Ar. P.	Archives de Physiologie.
Ar. P. M.	Archiv für die gesammte Physiol. des Menschen (Pflüger's).
Ar. P. N.	Archiv für Psychiatrie und Nervenkrankh.
Ar. P. P.	Archiv für exper. Pathologie und Pharmakologie.
Ar. Ped.	Archives of Pediatrics.
Ar. Ph.	Archives of Physiology.
Ar. R. R.	Archives of the Roentgen Ray.
Ar. S.	Archives of Surgery.
Ar. S. M.	Archivio per le Scienze mediche.
Ar. s. p.	Archives des Sciences physiques et naturelles.
Ar. T.	Archiv für wissenschaftliche und prak. Tierheilk.
Ar. V.	Archiv für Verdauungskrankheiten.
Arb. M.	Arbeiten aus dem med.-klin. Inst. zu München.
B. A.	Berlin Akademy.
B. A. P.	Beiträge zur Anat. und Physiologie.
B. B.	Berichte der Bayer. Akad. der Wissen.
B. C.	Biologisches Centralblatt.
B. C. G.	Berichte aus der Chemische Gesell.
B. d.	Berichte der deutsche pharm. Gesell.
B. D. N.	Berichte der Dorpater Naturforsch. Gesell.
B. J.	Biochemical Journal.
B. J. C. D.	British Journal of Children's Diseases.
B. J. D.	British Journal of Dermatology.
B. K.	Berliner Klinik. Sammlung klin. Vorträge.
B. K. T.	Beiträge zur Klinik der Tuberkulose.
B. k. W.	Berliner klinische Wochenschrift.
B. M. J.	British Medical Journal.
B. M. R.	Birmingham Medical Review.
B. M. & S. J.	Boston Medical and Surgical Journal.
B. M. v.	Bulletin de la Soc. centr. de Méd. vét.
B. p. G.	Berlin phys. Gesellschaft.
B. roy. M.	Bulletin de l'Académie roy. de Médecine.
B S. A.	Berichte der Sächs' Akademy.
B. S. P.	Bulletins et Mémoires de la Soc. anat. de Paris.
Be. A. P.	Beiträge zur pathol. Anat. (Zeigler).

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Be. C.	Beiträge zur klin. Chirurgie.
Be. P. P.	Beiträge zur chem. Physiol. und Pathol. (Hofmeister).
Bel. m.	Belge médical.
Bi. C.	Biochemisches Centralblatt.
Bib. M.	Bibliotheca medica.
Bio. C.	Biophysikalisches Centralblatt.
Bo. G.	Bollettino della r. Accad. med. di Genova.
Br. M.-C. J.	Bristol Medico-Chirurgical Journal.
Brain.	Brain.
Bu. g. t.	Bulletin général de Thérapeutique.
Bu. H.	Bulletins et Mémoires de la Soc. méd. d. Hôp. de Paris.
Bu. J. H. H.	Bulletin of Johns Hopkins Hospital.
Bu. L.	Bullettino della Soc. Lancisiana degli Ospedali di Roma.
Bu. M.	Bulletin médical, Le.
Bu. P.	Bulletin de l'Acad. de Médecine (Paris).
Bu. R.	Bullettino della Reale Accademia med. di Roma.
C. a. P.	Centralblatt für allgemeine Pathologie.
C. B.	Chemisches Berichte.
C. C.	Centralblatt für Chirurgie.
C. G.	Centralblatt für Gynäkologie.
C. H.	Centralblatt für Haut- und Geschlechtskr.
C. i. M.	Centralblatt für innere Medicin.
C. J.	Clinical Journal.
C. J. M.	Cleveland Journal of Medicine.
C. K.	Centralblatt für die Krankh. d. Harn- und Sex. Org.
C. k. m.	Centralblatt für klinische Medicin.
C. M.	Centralblatt für d. gesammte Medicin.
C. M. i.	Clinica medica italiana.
C. M. Pa.	Clinica medica gener. di Parma.
C. m. W.	Centralblatt für die medicinischen Wissenschaft.
C. N.	Centralblatt für Neurologie.
C. P.	Centralblatt für Physiologie.
C. r. A. M.	Compte-rendu de l'Acad. de Médecine.
C. r. A. S.	Comptes rendus de l'Académie des Sciences.
C. r. S. B.	Comptes rendus des Séances et Mém. de la Soc. de Biologie.
C. S.	Centralblatt für Stoffwechsel und Verdauungs-krankh.
C. s. A.	Correspondenz-Blatt für schweizer Aerzte.
C. St.	Clinical Studies (Bramwell).
C. Z.	Chemisches Zeitung.
Ch. An.	Charité Annalen.
Cl. M.	Clinica moderna, La.
Co. M.	Congrès français de Médecine.
Ct.B.	Centralblatt für Bakteriologie.
Ct. P. S.	Centralblatt für d. ges. Phys. u. Path. des Stoffwechsel.
Ct. T.	Centralblatt für gesammte Therapie.
D. A.	Dubois Archiv.
D. Ar. M.	Deutsches Archiv für klin. medicin.
D. J. M. S.	Dublin Journal of Medical Science.
D. K.	Deutsche Klinik.
D. m. W.	Deutsche medicinische Wochenschrift.
D. M.-Z.	Deutsche Medizinal-Zeitung.

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D. Z.	Deutsche Aerzte-Zeitung.
D. Z. C.	Deutsche Ztschr. für Chirurgie.
D. Zt.	Dermatologisches Zeitschrift.
E. A.	Experimental Archiv.
E. H. R.	Edinburgh Hospital Reports.
E. M. J.	Edinburgh Medical Journal.
Eng. A.	Engelmann's Archiv.
Er. P.	Ergebnisse der Pathologie (Lubarsch u. Ostertag).
Er. Ph.	Ergebnisse der Physiologie (Ascher u. Spiro).
F. B.	Festschrift für Bischoff.
F. h.	Folia hæmatologia.
F. L.	Finska Läkarsällskapet's Handlingar.
F. M.	Fortschritte der Medicin.
F. P.	Florence Labor. de Physiol. Résumé des Travaux.
G. m. B.	Greifswalder medicinische Beiträge.
G. M. C.	Mitteil. a. d. Grenzgebieten der Med. und Chir.
G. M. J.	Glasgow Medical Journal.
G. m. P.	Gazette médicale de Paris.
G. O.	Gazzetta degli Ospedali.
G. O. C.	Gazzetta Ospedali e Clin.
G. T.	Gazzetta medica di Torino.
Ga. H.	Gazette des Hôpitaux.
Gi. i. S.	Giornale internaz. d. Scienze med.
Gi. M. v.	Giornale ital. della Mal. ven. e della pelle.
Gi. T.	Giornale d. reale Accademia di Med. du Torino.
Gu. H.	Guy's Hospital Reports.
Gz. H.	Gazette hebdomadaire.
H.	Hospital.
H. C.	Hygienisches Centralblatt.
H. R.	Hygienisches Rundschau.
H. S. / Hos.	Hospitalstidende.
I. D. C.	International Dermatological Congress.
I. M. C.	International Medical Congress.
I. R.	Internationale klinische Rundschau.
I. T. C.	International Tuberculosis Congress.
In. C.	International Clinics.
In. C. L.	Internat. Centralb. f. Laryngologie.
J. A. M. A.	Journal of the American Medical Association.
J. A. P.	Journal de l'Anatomie et de la Physiologie.
J. A. & P.	Journal of Anatomy and Physiology.
J. B. C.	Journal of Biological Chemistry.
J. B. & C.	Journal of Balneology and Climatology.
J. C.	Journal of the American Chemical Society.
J. C. D.	Journal of Cutaneous and Gen.-Urin. Diseases.
J. D. S.	Journal de Dermat. et de Syphil.
J. E. M.	Journal of Experimental Medicine.
J. H. H. R.	Johns Hopkins Hospital Reports.

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J. Hy.	Journal of Hygiene.
J. La.	Journal of Laryngology, Rhinology, and Otology.
J. M.	Journal des Maladies Cutan. et Syph.
J. M. B.	Journal de Médecine de Bordeaux.
J. M. R.	Journal of Medical Research.
J. M. Sc.	Journal of Mental Science.
J. mil.	Journal de Médecine militaire.
J. N. & M.	Journal of Nervous and Mental Disease.
J. O. & G.	Journal of Obstetrics and Gynæcology of the British Empire.
J. P.	Journal of Physiology.
J. P. & B.	Journal of Pathology and Bacteriology.
J. P. C.	Journal für prakt. Chemie.
J. P. P. G.	Journal de Physiologie et de Pathologie générale.
Ja. G.	Jahrbücher über Gynäkol. und Geburtsch.
Ja. H.	Jahrbücher d. Hamburgischen Staatskrank.
Ja. K.	Jahrbücher für Kinderheilkunde.
Ja. M.	Jahrbücher der in- und auslandischen gesammte Med. (Schmidt).
Jan.	Janus.
Jb. L. M.	Jahresbericht ü. d. Leistungen u. Fortschr. in d. ges. Med.
Jb. L. O.	Jahresber. u. d. Leist. u. Fortschr. in Gebiete der Ophth.
Jb. T.-C.	Jahresber. u. d. Fortschr. der Thier-Chemie.
Jo. B.	Journal de Médecine (Bruxelles).
Jo. P.	Journal de Pharmacie et de Chimie.
K. i. M.	Kongress für innere Medicin.
K. J.	Klinisches Jahrbüch.
K. S.	Korrespondenz-Blatt für Schweizer Aerzte.
K. T. W.	Klinische-Therapeutische Wochenschrift.
K. V.	Korrespondenz-Blätter d. allg. ärztl. Vereins von Thüringen.
K. W.	Korrespondenzbl. d. Württemb. ärztl. Landesv.
L.	Lancet.
L. m.	Lyon médical.
La. R.	Laboratory Reports, Roy. Coll. Phys., Edinburgh.
Li. M.-C. J.	Liverpool Medico-Chirurgical Journal.
M.	Morgagni, Il.
M. A. B.	Mémoires de l'Acad. roy. de Belgique.
M.-C. T.	Medico-Chirurgical Transactions.
M.-C. U.	Medicin.-Chemische Untersuchungen.
M. Chr.	Medical Chronicle.
M. H.	Middlesex Hospital.
M. i.	Médecine infant., La.
M. K.	Medicinische Klinik.
M. M.	Medical Magazine.
M. m.	Médecine moderne, La.
M. M. J.	Montreal Medical Journal.
M. N.	Medical News.
M. N. A.	Memoirs of the National Academy of Sciences.
M. O. A.	Magyar Orvosi Archivum.
M. R.	Medical Record.
M. Rev.	Medical Review.
M. T.	Medical Times and Gazette.
Ma.	Maly's Jahrbuch.

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Mit. B.	Mitteilungen aus der Berlin phys. Gesell.
Mit. H.	Mitteilungen aus der Hamburg. Staatskrankenanstalten.
Mit. K.	Mitteilungen aus der med. Klinik zu Königsberg.
Mit. U.	Mitteilungen der Kgl. Ges. d. Wiss. zu Upsala.
Mit. W.	Mitteilungen aus der med. Klinik zu Würzburg.
Mo. C.	Monatsschrift für Chemie.
Mo. D.	Monatshefte für praktische Dermatologie.
Mo. G. G.	Monatsschrift für Geburtsch. und Gynäkologie.
Mo. K.	Monatsschrift für Kinderheilkunde.
Mo. m.	Montpelier médical.
Mo. U.	Moleschotts Untersuch. zur Naturlehre.
Mü. m. W. Mu. m. W.	Münchener med. Wochenschr.
N. A. S.	Memoirs of the National Academy of Sciences.
N. B.	von Noorden's Beiträge.
N. C.	Neurologisches Centralblatt.
N. C. T.	Nuova clin. terap., La.
N. I. S.	Nouvelle Iconographie de la Salpêtrière.
N. k. A.	von Noorden's klinische Abhandlung.
N. m. A.	Nordiskt medicinskt Arkiv.
N. T.	Nederlandsch Tijdschrift voor Geneeskunde.
N. V.	Naturw. Verein. f. Neuvorpommern.
N. Y. J.	New York Medical Journal.
N. Y. M.	New Yorker medicinische Monatssch.
N. Y. & P. J.	New York and Philadelphia Medical Journal.
P.	Policlinico, Il.
P. L.	Przeglad Lekarski.
P. m.	Presse médicale, La.
P. m. b.	Presse médicale belge, La.
P. M. J.	Philadelphia Medical Journal.
P. P. C.	Proceedings of the Philadelphia County Medical Society.
P. R.	Proceedings of the Royal Society (London).
P. R. Ed.	Proceedings of the Royal Society of Edinburgh.
P. T.	Philosophical Transactions of the Royal Society.
P. V.	Prager Vierteljahrsschr.
P. W.	Prager medizinische Wochenschrift.
Pa. M. T.	Philadelphia Medical Times.
Ped.	Pediatria, La.
Pr.	Practitioner.
Pro. M.	Progressive Medicine.
Pro. mé.	Progrès médical, Le.
R. c.	Revista clinica.
R. c. c.	Rivista critica clinica.
R. c. M.	Rivista gén. ital. di clin. med.
R. c. P.	Rivista di clin. Pediatr.
R. c. t.	Revue générale de clinique et thérapeutique.
R. M.	Riforma medica.
R. M. E.	Revue mensuelle des Mal. des Enfance.
R. m. M. C.	Revue mensuelle de Méd. et Chir.
R. m. R.	Russische medicin. Rundschau.
R. N. P.	Review of Neurology and Psychiatry.

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R. P.	Russische Arch. der Pathologie.
R. T.	Revue de Thérapeutique.
R. v.	Rivista veneta di Scienze mediche.
R. Z. D.	Russische Ztschr. f. Dermat.
Re. C.	Revue de Chirurgie.
Re. Gy.	Revue de Gynécologie et Chir. abdom.
Re. M. / Re. m.	Revue de Médecine.
Ri. c.	Rivista clinica e terapeutica.
Riv. M.	Rivista di medicina.
S.	Sperimentale, Lo.
S. B.	Société de Biologie.
S. b. A.	Sitzungsber. d. königlich-bayer. Akad. d. Wiss. zu Münch.
S. E.	Sitzungsber. der physikal.-med. Soc. zu Erlangen.
S. J.	Scottish Medical and Surgical Journal.
S. K.	Sitzungsber. d. Kaiserl. Akad. d. Wissen. (Math.-natur. Kl.).
S. M.	Sitzungsber. d. Gesell. f. Morphol. u. Physiol. zu München.
S. m. A.	Sammlung med. Abhandlung.
S. m. H.	Société méd. d. Hôpitaux.
S. n. G.	Sitzungsber. d. niederrh. Gesell. f. Natur.- und Heilkunde.
S. W.	Sitzungsber. d. phys.-med. Gesell. zu Würzburg.
S. W. A.	Sitzungsber. d. Kaiserl. Akad. d. Wissen. (Math.-natur. Kl.).
S. W. D.	Sitzungsber. d. Wien dermat. Gesell.
Sc. W.	Schweiz Wchnschr. f. Chem. u. Pharm.
Se. M.	Semaine médicale.
Set. M.	Settimana medica, La.
Sit. M.	Sitzungsber. d. Gesell. z. Beforderung d. Ges. Nat. z. Marburg.
Sk. Ar. P.	Skandinavisches Archiv für Physiologie.
St. B. H.	St. Bartholomew's Hospital.
St. B. J.	St. Bartholomew's Hospital Journal.
St. P.	St. Petersburger medicin. Wochenschr.
St. T. H.	St. Thomas's Hospital.
T. A. A. P.	Transactions of the Association of American Physicians.
T. A. S. A.	Transactions of the American Surgical Association.
T. C. P. P.	Transactions of the College of Physicians of Philadelphia.
T. Cl. S.	Transactions of the Clinical Society of London.
T. Co. A. P.	Transactions of the Congress of American Physicians and Surgeons.
T. F.	Travaux du Laboratoire de L. Frédéricq.
T. G.	Therapie de Gegenwart.
T. M.	Therapeutische Monatshefte.
T. M. S.	Transactions of the Medical Society of London.
T. O. S.	Transactions of the Obstetrical Society of London.
T. P. S.	Transactions of the Pathological Society of London.
Th. G.	Therapeutic Gazette.
U. A. M.	Ungarisches Archiv für Medizin.
U. m.	Union médical, L'.
U. M. M.	University Medical Magazine.
U. P.	Ungarische Medizin.-chir. Presse.
U. Pa.	University of Penna. Med. Bulletin.
U. S. D. B.	United States Department of Agriculture Bulletin.

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V. b. A.	Verhandl. d. böhmischen Akad. der Wissensch.
V. B. M.	Verhandl. d. Berliner medicin. Gesell.
V. C. M.	Verhandl. d. Congresses f. inn. Med.
V. d. G.	Verdandl. d. deutschen pathol. Gesell.
V. f. A.	Verhandl. d. finnischen Aerzte.
V. G. K.	Verhandl. d. Gesell. f. Kinderh.
V. i. M.	Verein für innere medicin zu Berlin.
V. K. D.	Verhandl. d. Kongr. d. d. Dermat. Gesell.
V. n. A.	Verhandl. d. d. naturfors. u. Aerzte.
V. n. G.	Verhandl. d. naturforsch. Gesell. in Basel.
V. n. V.	Verhandl. d. Naturf.-Versamm. in Meran.
V. p. G.	Verhandl. d. physiol. Gesell. in Berlin.
V. s. G.	Verhandl. d. Schles. Gesell. f. vaterl. Kultur.
V. W. G.	Verhandl. d. phys.-med. Gesell. in Würzburg.
Vo. s. V.	Volkmann's Sammlung klin. Vorträge.
W.	Wratsch.
W. A.	Wiener Akademie.
W. Ab.	Würzburger Abhandl. a. d. Gesam. der prak. Heilk.
W. J.	Wiener medicinische Jahrbücher.
W. K.	Wiener Klinik: Vortr. a. d. gesamm. prak. Heilk.
W. k. R.	Wiener klinische Rundschau.
W. k. W.	Wiener klinische Wochenschrift.
W. L. J.	West London Medical Journal.
W. m. B.	Wiener medicinische Blätter.
W. m. P.	Wiener medicinische Presse.
W. m. W.	Wiener medicinische Wochenschrift.
W. V.	Würzburger Verhandlungen.
W. Z.	Wiener Zeitschrift.
Y. J.	Yates and Johnson Laboratory Reports.
Z. a. C.	Zeitschrift für anal. Chemie.
Z. a. P.	Zeitschr. f. allg. Physiologie.
Z. B.	Zeitschr. f. Biologie.
Z. C.	Zeitschr. f. angewandte Chemie.
Z. d. p. T.	Zeitschr. f. diätet. und physikal. Therapie.
Z. e. P.	Zeitschr. f. exper. Pathologie.
Z. G. G.	Zeitschr. f. Geburtsch. u. Gynäkol.
Z. H.	Zeitschr. f. Heilkunde.
Z. Hy.	Zeitschr. f. Hygiene.
Z. M.	Zeitschr. f. klin. Medicin.
Z. N.	Zeitschr. f. Nervenheilkunde.
Z. P.	Zeitschr. f. Psychologie.
Z. P. A.	Zeitschr. f. allg. Pathol. und path. Anat.
Z. p. A.	Zeitschr. f. prakt. Aerzte.
Z. P. C. / Z. p. c.	Zeitschr. f. physiol. Chemie.
Z. r. M.	Zeitschr. f. rationelle Medizin.
Z. T.	Zeitschr. f. Tuberkulose.
Z. V.	Zeitschr. f. Vatermarkande.
Ze. P. P. S.	Zentralbl. f. d. gesamm. Physiol. und Path. d. Stoffwech.

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THE PATHOLOGY OF METABOLISM

CHAPTER I

FASTING AND CHRONIC STARVATION

By K. von NOORDEN

Translated by A. J. Jex-Blake, M.A., M.B.

A knowledge of the metabolism during fasting is of great importance for both physiology and pathology; the former owes many important discoveries to experiments made upon fasting animals and men, while the latter has to do with diseased persons who are starving or nearly so.

The changes in the metabolism produced by sickness cannot be determined without a knowledge of the changes due to simple inanition. Ignorance of this fact has led inquiry into many a wrong track for years. Instances of this are the question of the breaking down of protein in fever or in diabetes, and the problem of the chlorine changes in aceto-nuria.

It is of practical importance to distinguish between two forms of fasting:

1. Acute starvation, or the sudden complete withdrawal of food after a period of good nutrition.

2. Chronic starvation, or malnutrition, depending upon weeks or months of continuously insufficient nutrition.

Science has hitherto devoted most attention to the former, which has been accurately studied. Particular reference may here be made to the comprehensive work of C. Lehmann, Fr. Müller, J. Munk, H. Senator, and N. Zuntz, who made their experiments upon two well-known fasting men, Cetti and Breithaupt.

But chronic starvation has not yet been investigated so thoroughly. The pathology of its metabolism is still sensibly incomplete, though many additions have been made to it during the last few years. Patients are often met with on the bed of sickness whose intake of combustible food has been less, over long periods of time, than their expenditure of it, and who have in consequence extensively injured their state of nutrition.

We propose to consider both these forms of starvation.

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1. The Consumption of Energy.

(a) *On the Complete Withdrawal of Food.*

During the first few days of acute starvation the general metabolism suffers no diminution, other things being equal [v. Hoesslin (2), Lehmann and Zuntz (1), Rubner (3), Johansson (4)]. In other words, the body uses up the same amount of material, and lives thriftlessly at the expense of its own tissues for want of any other food-supply.

Classical examples of this are the experiments made upon a watchmaker by C. Voit and Pettenkofer, and by Ranke upon himself (5).

During twenty-four hours of light work the watchmaker converted—

When starved .. .. 2,320 calories (mean of 2 experiments).
When fed .. .. 2,362 „ („ 7 „).

During twenty-four hours of bodily repose Ranke converted—

When starved .. .. 2,150 calories (mean of 3 experiments).
When fed .. .. 2,449 „ („ „ „).

Thus the decomposition of material on food days was but little greater than it was during days of starvation. The increase explains itself at once as due partly to the work of digestion, and partly to the additional decompositions that follow the consumption of any food. Rubner (6) calculates that the energy consumed by persons on an average diet (diet of maintenance) is generally only 7 to 8 per cent. greater than it is during starvation. Magnus-Levy (7) calculates that the upper limit of the difference may be regarded as about 15 per cent.

The older researches dealt with single days of starvation only. More protracted and very accurate experiments have been conducted by Tigerstedt (4) and his assistants, with the use of a Pettenkofer's respiration apparatus. They concern a student, twenty-six years of age, who passed his time in the respiration chamber during the whole course of the experiments with the exception of two hours a day.

Day of Fast.	*Calories from Protein.*	*Calories from Fat.*	*Total of Calories.*	*Weight (Kg.).*	*Calories per Kg.*
1	303·5	1916·9	2220·4	66·99	33·15
2	320·5	1781·9	2102·4	66·71	32·00
3	339·4	1684·7	2024·1	64·88	31·20
4	341·4	1651·9	1992·3	63·99	31·13
5	286·1	1684·7	1970·8	63·13	31·23

Here it is seen that the absolute amount of the metabolism diminished notably up to the fifth day. But if the figures are calculated with reference to the body-weight, as is indispensable in view of the progressive diminution in the amount of the active protoplasm, then fairly constant figures are obtained (see the last column).

From a comparison of all the known determinations of the liberation

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of heat in starving men and animals, the following law may be deduced: The expenditure of energy during starvation diminishes in the same proportion as the weight of the body [Rubner (8)]. Apart from extreme degrees of emaciation or adiposity, and with moderate bodily exercise by day and normal hours of sleep by night, the daily expenditure of energy by fasting persons is to be reckoned at a rate of 30 to 32 calories per kilogramme [E. Voit (9), Rubner (8)].

The values are naturally smaller when the fasting person submits to complete repose so far as all voluntary movements are concerned. Under these circumstances the threshold value for the expenditure of energy is obtained—the so-called minimal metabolism or fundamental conversion of potential energy into heat.

Researches having reference to single days only gave the following results:

Weight (Kg.).	*Calories Converted.*	*Calories per Kg.*	*Observer.*
56·5	1,477	26·1	Magnus-Levy (10).
69·45	1,480-1,507	21·3-21·70	Zuntz [1]
(?)	(?)	21·72	Johansson [2]
49·5	1,221	24·69	Tigerstedt [3]
(?)	(?)	22·8	W. O. Atwater [4]

Also the experiments on Cetti and on Breithaupt give figures for the fundamental conversion during complete bodily repose. In the case of Cetti—

Day of Fast.	*Calories.*	*Calories per Kg.*
1st to 4th	1618·0	29·00
5th and 6th	1504·7	28·38
7th and 8th	1602·0	31·74
9th and 10th	1508·5	29·26

In the case of Breithaupt the figures obtained were—

	Calories.	*Calories per Kg.*
Two days of feeding before the fast ..	1645·2	27·35
Mean of six fasting days	1550·4	26·81
Fifth and sixth fasting days	1292·2	22·79
Two days of feeding after the fast	1453·2	24·79

The figures given by Luciani (13) for Succi—that artist in fasting—agree well with Cetti's and Breithaupt's, though they do not lay claim to the same accuracy, owing to the faulty experimental methods employed in their determination.

Taken together, the preceding investigations lead to the general value of 22 to 25 calories per kilogramme per day as the mean minimum conversion of energy while fasting during complete bodily rest. The figures are of theoretical rather than practical interest, for complete repose is never maintained excepting during coma or in deep hysterical or hypnotic sleep. Practically speaking, the figures given previously are far more important.

[1] Quoted by Johansson.
[2] Experiment on himself.
[3] Fifth day of fast of a woman in hysterical sleep.
[4] Experiment during sleep.

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The investigations on Cetti, Breithaupt, and Succi, in agreement with earlier determinations made upon animals [Regnault and Reiset (14), Finkler (15), etc.], show, further, that during repose the excretion of CO_2 diminishes more rapidly than does the consumption of O_2, as the respiratory quotient proves.

The fasting man lives upon protein and fat, excepting during the first few days while his muscles and liver still contain glycogen. In consequence, the respiratory quotient falls from the height (1·0)—indicating the combustion of carbohydrate—to approach the values indicating the consumption of protein or fat (0·809 to 0·707). The more abundantly the fasting person is fed beforehand, the greater is his supply of glycogen when the fast begins, and the more slowly will his respiratory quotient diminish. This explains the difference, observed during the first few days of fasting, between the well-fed Breithaupt and the less well-nourished Cetti (see the table below).

The fact that the respiratory quotient at times fell below the theoretical minimum 0·7 demands special explanation. It depends upon the consideration that during fasting a certain quantity of carbon-containing compounds (acetone, aceto-acetic and β-oxybutyric acids) are excreted in the urine in addition to the loss of CO_2 from the lungs. And, further, Lehmann and Zuntz (1) have correctly concluded that during repose and abstinence from all voluntary movements small quantities of glycogen arising from the decomposition of protein collect in the liver and muscles. If this is so, muscular work, which increases the decomposition of glycogen, must increase the respiratory quotient. As a matter of fact, experiments made upon Breithaupt during work led to this result. Luciani obtained similar figures with Succi; the respiratory quotient fell below 0·7, averaging 0·685 between the twelfth and thirtieth days of his fast. This is the more remarkable because Luciani's experimental method is not entirely free from objection, and leads to figures that are too high rather than too low.

Pembrey and Spriggs record that in rats during fasting the respiratory exchange quickly reaches a minimum, and remains almost constant during the prolongation of the fast. The respiratory quotient falls to 0·75 or even to 0·63, the figures below the theoretical value being explained by the conversion of fat into glycogen and sugar (15A).

Day of Fast.	*Cetti.*			*Breithaupt.*		
	Per Kg. and Minute.			Per Kg. and Minute.		
	O_2.	CO_2.	Respiratory Quotient.	O_2.	CO_2.	Respiratory Quotient.
1	4·86	3·51	0·72	3·96	3·48	0·87
2	4·59	3·13	0·68	4·32	3·19	0·74
3	4·48	3·07	0·68	4·26	3·12	0·73
4	4·78	3·10	0·65	4·38	3·19	0·73
5	4·68	3·10	0·66	4·37	2·75	0·63
6	4·67	3·13	0·67	3·45	2·26	0·86
7	5·06	3·39	0·67	3·76	2·60	0·69
8	4·89	3·33	0·68	4·07	2·94	0·72
9	4·62	3·10	0·67	—	—	—
10	4·67	3·16	0·68	—	—	—

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(*b*) *Consumption of Energy in Chronic Starvation.*

It is of more practical importance to know whether the laws given above for acute starvation also hold good in chronic malnutrition. An individual in a condition of poor nutrition through insufficient feeding might then indulge in extravagant metabolism as he does in acute starvation. On the other hand, he might establish a sort of automatic and purposive regulation, diminishing the amount of his metabolism when placed on a continuously inadequate diet. And here arises a question of some clinical importance : What is the amount of food necessary to maintain patients who are markedly emaciated ? The few investigations bearing on this point have been made by varied methods, and indicate that regulation of the expenditure of energy is possible to a moderate extent.

C. Voit (16) found that a man weighing 43 kilogrammes, who had sunk into a very low state in consequence of a gastritis that prevented him from taking proper nourishment, had a daily metabolism equal to 1,266 calories (= 29·4 calories per kilogramme). Later his nutrition improved ; he then weighed 57 kilogrammes, and his metabolism rose to 2,059 calories (= 36·1 calories per kilogramme). Pettenkofer and Voit found that a weakly, underfed tailor, aged thirty-six, metabolized at the rate of only 29·8 calories per kilogramme (1,568 calories, weight 52·5 kilogrammes). And v. Rechenberg (17) found that among the badly-nourished weavers of Saxony the rate of metabolism had fallen to 29 calories per kilogramme in certain instances. Seeing that the subjects of the experiments in the Pettenkofer's respiration apparatus did not suppress all voluntary movements, and that v. Rechenberg's weavers continued to do their work (which is certainly not heavy), one might reasonably expect that on an average diet their metabolism would be at a rate of 34 or 36 calories per kilogramme.

E. Buys (18) gives a remarkable account of a labourer weighing 72 kilogrammes. His diet was habitually scanty, and particularly poor in protein. Buys calculates that the heat value of his whole diet for three separate periods of three days each amounted to 1,600 calories gross (= about 22 calories per kilogramme). This was the man's " diet of maintenance " ; his urine contained an average of 6·3 grammes of nitrogen per day. But the shortness of the periods of observation detracts much from the value of Buys' figures.

Clinical experience is naturally of great importance here. Fr. Müller (19) investigated the metabolism of a patient with œsophageal stenosis, due to the swallowing of caustic alkali, during a period in which she improved. Her weight was 31 kilogrammes at the outset, and was increased during observation by 3½ kilogrammes, of which 1½ kilogrammes represented true increase of tissue.[1] Her food for the first five days

[1] G. Klemperer (21) recorded a case that has been much quoted. A tailoress, aged twenty-two, was improperly fed, and her weight fell from 50 to 36 kilogrammes ; for eleven days she remained in nitrogen equilibrium at 18 calories per kilogramme. Klemperer concluded that, as she was in nitrogen equilibrium, his patient was also in heat

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represented a maximum of 24·7 calories per kilogramme per day, for the next seven days 27·1 calories, and for eight more days 30 calories. A similar case is recorded by A. Nebelthau (20).

I can record the case of a sempstress, aged twenty-one, who came under my treatment for obstinate hysterical vomiting. Before this time she had lapsed into a bad state in consequence of repeated vomiting, which came on after every attempt to take food. For the first fourteen days of her treatment she was unable to absorb sufficient nutriment, so that her weight sank from 42 to 38 kilogrammes. She then began to retain milk given to her in small quantities, and during the next sixteen days took 1,500 c.c. of milk a day; every attempt to increase this quantity miscarried. During these sixteen days her weight increased by 1,900 grammes, so that her diet of maintenance appeared to be less than 950 calories (= 25 calories per kilogramme of her original weight). The milk given contained 8·1 grammes of nitrogen, 5·2 grammes of which were excreted in the urine and 0·9 gramme in the fæces. The patient lay in bed, bestirring herself with moderate activity.

A certain amount of care must be exercised in the use of these figures derived from marantic patients. It must be remembered that during the antecedent period of malnutrition most of them had not only lost from the solid constituents of their bodies, but had also parted with much fluid from their blood and tissues. The increase in body-weight may have been due to retention of water, and may conceal an actual loss of fat. Thus it is not certain that the food-stuffs supplied did really cover the indicated conversion into energy. Hence only extended series of observations must be taken as proof positive.

More trustworthy evidence may be obtained by respiration experiments. F. Kraus (22) found that the O_2 consumption of a marantic patient was not lessened (Observations, Nos. 5, 10, and 11). Svenson (23), on the other hand, concluded that persons debilitated by protracted and severe typhoid fever used up a subnormal amount of energy. Further evidence is required; it seems doubtful whether the convenient method of Geppert-Zuntz will prove satisfactory here. In any case single isolated determinations are insufficient, as absolute and not comparative figures are wanted, and so long sequences of experiments are essential. A certain length of time is always necessary in order to accustom the patient to the experimental conditions before correct figures can be obtained from him.

Reviewing the foregoing results, it cannot at present be denied that certain isolated individuals are able to exist with a particularly low

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equilibrium, so that her "diet of maintenance" would be at the rate of 18 calories per kilogramme per day. But this is inadmissible. The only conclusion justified by the observation is this: that after protracted malnutrition the organism can retain nitrogen to build up the cells demanding protoplasm even when on a scanty nitrogen diet. The loss in body-weight shows clearly that the patient's diet was far too low, and that she added to it from her own fat; for in the eleven days her weight fell from 36·1 to 34·8 kilogrammes.

It is necessary for me to lay particular stress on the inadmissibility of Klemperer's deduction here, because nitrogen equilibrium, or the putting on of nitrogen, is still being taken as evidence of an adequate supply of calories even up to the present time.

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consumption of energy; this may be due to some special disposition of their protoplasm, or to habit, or to long lasting malnutrition dependent upon some exhausting disease. But it is possible that the opinion I have expressed and supported elsewhere is correct. I believe that, even in chronic starvation, the minimal energy required by persons who are bedridden, or who are indoors and do little bodily work, does not fall below 30 to 32 calories per day per kilogramme. This always involves a certain diminution in the production of heat, since these caloric values concern bodies that are poor in fat.

Rubner (25) has recently investigated the consumption of energy in chronically ill-fed animals. Speaking generally, the consumption grew less and less during malnutrition; it remained nearly constant if calculated relatively to the weight or to the surface-area of the body. Rubner attributes exceptions to "a circumstance dependent upon the numerous influences summed up in what we call Individuality."

In view of the want of extended observations upon man, it is worth while to quote Rubner's figures for a dog, whose consumption of energy was investigated for three years.

Variations in Weight.	*Mean Weight.*	*Average Conversion of Calories.*	*Average Conversion of Calories per Kg.*
Kgm.			
7·01–6·84	6·94	432·1	62·3
6·66–6·33	6·45	371·8	57·6
6·27–5·80	6·09	332·0	54·7

Here, then, a diminishing conversion of calories per kilogramme accompanies a progressive loss of weight. For the present it must be left an open question whether this is due to diminished muscular activity following bodily debilitation [Rubner], or to diminished activity of protoplasm which has adapted itself to the necessities of its case.

2. Protein Metabolism in Fasting.

(*a*) *During Complete Starvation.*

The protein metabolism of man during acute starvation has been investigated many times. Fasting persons habitually take water in small quantities, usually refusing larger amounts. The changes in the protein decomposition are best seen in the following table, which gives the nitrogen-content of the urine. The protein decomposition can be reckoned by multiplying this figure by 6·25, after adding to it 0·2, which is the daily nitrogen-content of the fæces, or, actually, the mean of the figures obtained from Cetti and Breithaupt—0·316 and 0·113 gramme nitrogen (1).

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Day of Fast.	*Cetti,* 57·0 *Kg.*	*Breithaupt,* 60·07 *Kg.*	*Succi, I.* (1), 62·4 *Kg.*	*Succi, II.* (26), (?) *Kg.*	*Tigerstedt* (4), 70·0 *Kg.*	*Hooven-Sollmann* (27), 58·5 *kg.*
1	13·5	10·0	13·8	17·0	12·2	21·0
2	12·6	9·9	11·0	11·2	12·8	12·4
3	13·1	13·3	13·9	10·5	13·6	12·4
4	12·4	12·8	12·8	10·8	13·7	14·0
5	10·7	10·9	12·8	11·2	11·5	14·0
6	10·1	9·9	10·1	11·0		14·0
7	10·9		9·4	8·8		10·8
8	8·9		8·4	9·7		14·5
9	10·8		7·8	10·0		
10	9·5		6·8	7·1		
11			7·9	6·3		
12			7·2	6·8		
13			3·5	5·1		
14			5·3	4·7		
15			5·1	5·0		
16			5·5	4·2		
17			6·2	5·4		
18			5·5	3·6		
19			5·5	5·7		
20			4·4	3·3		
21			3·9	2·8		

All these figures were obtained from full-grown men who were in a good state of nutrition when they began to fast. After the first, or perhaps after the first two days (see below), the standard daily loss of nitrogen may be taken as 10 to 13 grammes for the next week or ten days. The only figures that are larger than this, which is supported by other observations, are those of Hooven-Sollmann, who worked with a thin, but very muscular man. Exact references to the body-weight cannot be given in the experiments made upon fasting men, since the daily nitrogen loss calculated with reference to the daily body-weight varies somewhat widely. But the following average rule, in agreement with numerous experiments upon animals, may be stated : the loss of nitrogen is relatively greater in the thin than in the fat, in the small than in the large [Prausnitz (33)].

From 1 kilogramme of the daily body-weight the nitrogen in the urine was :

Day of Fast.	*Cetti.*	*Breithaupt.*	*Succi, I.*	*Tigerstedt.*	*Hooven-Sollmann.*
1	0·243	0·170	0·221	0·182	0·329
2	0·228	0·170	0·181	0·195	0·214
3	0·242	0·230	0·232	0·210	0·216
4	0·233	0·222	0·213	0·214	0·248
5	0·206	0·194	0·216	0·181	0·250
6	0·198	0·177	0·173		0·253
7	0·214		0·161		0·197
8	0·176		0·146		0·250
9	0·213		0·134		0·405
10	0·190		0·119		

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The nitrogen loss during starvation is lower in women than in men. No long and systematic investigations have been made on women, though satisfactory data for single days of starvation have often been published. F. Müller (28) found that in a well-nourished patient with hallucinatory insanity the nitrogen elimination for the first four days of starvation averaged 6·5 grammes (= 0·141 gramme per kilogramme); in another case the nitrogen elimination from the fourth to the ninth day of fasting averaged 5·5 grammes (= 0·108 gramme per kilogramme).

In the case of a well-nourished melancholic aged thirty, who took weak coffee and weak broth freely, but no other food, I found the urinary nitrogen elimination from the second to the fifth day of her fasting to be 4·86, 7·39, 6·81, and 5·81 grammes (average = 6·22 grammes per diem = 0·107 gramme per kilogramme) (29). A well-nourished girl of twenty, who had injured her pharynx with caustic alkali, and refused all food, received thrice daily a rectal injection of dilute salt solution. The scanty fæces contained 0·25 gramme nitrogen per day; the urine yielded the following figures:

Day of Fast.	*Nitrogen in Urine.*	*Weight.*	*Nitrogen in Urine per Kg.*
	Gm.	Kg.	
1	10·1	62·1	0·161
2	7·3	16·3	0·119
3	8·0	60·7	0·131
4	6·7	59·8	0·112
5	6·2	59·0	0·105

Investigating a number of young women with gastric disorders, who were receiving no food for therapeutic reasons, my quondam assistant, L. Meyer, found:

Day of Fast.	1.	2.	3.	4.	5.	6.	
1	10·3	5·0	8·9	4·8	11·4	5·7	Grammes of nitrogen.
2	9·5	9·7	7·3	5·2	5·0	8·9	
3	9·4	—	8·5	4·7	—	11·0	
4	—	—	8·8	—	—	—	

Similar figures were obtained by A. Schäfer (30), who examined the nitrogen excretion of some fasting female lunatics for isolated periods of twenty-four hours.

Hence it appears that the nitrogen excretion of fasting women is from 20 to 30 per cent. less than that of fasting men.

These values are of great importance for the determination of the pathological decomposition of protein. If in a given case there is any essential divergence of the figures from the standard values, amounting to several grammes, the conclusion that there is here a pathological increase or decrease in the protein decomposition is justified. It must not be forgotten that the nitrogen excretion is usually just below the

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normal in old or fat patients, and just above normal in the young and lean.

To give examples :

I found that a woman with phosphorus-poisoning, while absorbing practically nothing from her food, excreted in her urine and fæces an average of 15·74 grammes nitrogen from the second to the sixth day, and an average of 14·55 grammes nitrogen from the seventh to the eleventh day.

Here, then, the amount of protein broken down was distinctly above the normal figure for starvation ; the conclusion is that the phosphorus-poisoning caused a pathological increase in the protein decomposition (31).

A girl, aged eighteen, with gastric disease, came under my treatment for gastric hæmorrhage. No food, either solid or liquid, was given to her, and on the three days following the hæmatemesis that brought her to the hospital we found 12·8, 17·8, and 20·1 grammes of nitrogen in the urine.

The law stated above would lead to the conclusion that the acute anæmia determined by the hæmorrhage—the hæmoglobin value of the blood was 68 per cent. on the second day—caused an increased breaking down of protein. But this conclusion would be wrong, for on the second and third days the patient passed large stools mixed with blood that contained 48 grammes of nitrogen (= about 1,300 c.c. blood). It is clear that large quantities of protein had been absorbed from the blood as it passed through the intestine, increasing the protein decomposition just as feeding with protein of any other kind would have done. In cases of sudden loss of blood where no absorption of protein takes place the breaking down of protein is far from being increased. I pointed this out first eleven years ago [v. Noorden (32)], and, in agreement with other investigators, must emphasize it once again.

In the determination of standard values the first two days of a fast must be carefully excluded, because the patient has not reached his proper inanitional rate of protein decomposition before they have passed. The nitrogen excretion of the first two days cannot lead to any broad conclusions. It is certain that the protein decomposition of the first day, and often of the second day too, depends not only upon the quantity of active protoplasm in the body and the degree of its activity, but also upon such peculiarities of the earlier nutritive conditions as the extent of the previous breaking-down of protein, or the quantity (whether large or small) of protein-sparing glycogen stored in the body. While present in quantity glycogen protects the protein to a certain extent. When the glycogen is used up it frequently, but not always, happens that the protein decomposition increases a little, then it sinks again slowly as the starvation continues and the body becomes poorer in protein.

This is the view of Prausnitz (33), and the majority of authors [May, Johansson, Landergren (34)] subscribe to it. It is natural that in certain cases the increase should be absent, particularly when the diet preceding the fast contains little carbohydrate. The following table records the chief of the figures at present available, excluding those given in earlier tables :

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Author.		*Last Day before Fast.*	*First Day of Fast.*	*Second Day of Fast.*	*Third Day of Fast.*	*Fourth Day of Fast.*
Prausnitz ..	1	9·3	7·8	13·0		
	2	8·1	4·6	4·4		
	3	16·8	11·9	10·6		
	4	12·2	9·6	13·0		
	5	12·0	13·3	11·0		
	6	7·8	9·9	10·3		
	7	—	9·3	12·5		
	8	15·3	14·0	14·9		
	9	18·6	12·9	13·8		
	10	16·2	7·9	14·5		
	11	12·4	7·7	12·6		
	12	16·9	13·3	16·0		
	13	13·9	8·2	14·9		
	14	—	11 7	13·0		
	15	23·1	17·3	19·0		
Landergren ..	—	9·7	13·6	13·4	15·1	13·8
Schreiber-Waldvogel (35) ..	1	7·1	8·8	10·1	11·7	—
	2	—	9·4	11·3	14·3	—
Edlefsen (36) ..		—	12·3	6·5	—	—
Sadowenne (37)		20·2	13·3	5·4	9·6	9·4

It should be noted that both in these shorter experiments and in those of longer duration it makes no difference to the nitrogen excretion whether water is or is not taken during the fast [Schäfer (30), Sadowenne (37)].

The protein decomposition is relatively large at first, and usually sinks somewhat sharply as the starvation proceeds. This fact clearly gives expression to the effort made by the organism to husband its valuable protein. A previous table shows the extremely low values found in the second halves of the two long fasts of Succi, and other isolated similar observations can be found in the literature. Some are given in the table below :

Author.	*Day of Fast.*	*Nitrogen in Urine.*	*Nitrogen per Kilogramme.*	*Patient.*
		Gm.		
Scherer (38) ..	28th	4·417	0·085	Female lunatic.
Schultzen (39) ..	15th and 16th	2·794	—	Female.
Seegen (40) ..	14th to 25th	4·15	—	—
Tuczek (4) ..	15th to 22nd	4·26	—	—
Tuczek (4) ..	9th to 28th	4·3	—	—

Similarly small values are met with in persons who begin to fast after a long period of insufficient nutrition, particularly if their supply of protein has been inadequate during this time. A young woman with œsophageal stenosis due to the swallowing of caustic alkali fell in weight from 45·5 to 34·5 kilogrammes in six weeks ; Fr. Müller (42) found her urinary nitrogen to be 4·92, 4·15, 3·25, and 3·01 grammes during four days of abstinence, the fæcal nitrogen averaging 0·446 gramme per day. The

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total nitrogen excretion was at the rate of 0·128 gramme per kilogramme per day.

I investigated the case of a girl of seventeen, whose weight had fallen from 51 to 35 kilogrammes, and who had taken only ⅓ to ½ litre of milk and diluted wine daily for five or six weeks on account of violent gastric pains. During three days, on which she took only fragments of ice, I found (43) 3·4, 3·3, and 2·9 grammes of nitrogen in her urine = 0·091 gramme per kilogramme per day, or 0·097 gramme with the correction for the fæcal nitrogen (43).

Nebelthau (44) records even smaller figures. A girl who had been insufficiently nourished for years on account of hysterical anorexia and hyperemesis, secreted no more than 1·53, 2·27, 1·65, and 1·97 grammes nitrogen (= 0·046 gramme nitrogen per kilogramme per day) during four days of fasting.

These figures show how the organism spares its protein when it is ill fed. This statement presupposes that the body has been distinctly impoverished as regards protein by the preceding malnutrition. If the feeding has been otherwise, then the fasting person decomposes protein without economy even after a period of pronounced malnutrition. An instance of this was furnished by a thin, slightly muscular man fifty-two years of age, who suffered from hypochondria and indigestion, but had no actual disease of the digestive tract. He considered that the following daily diet, on which he had lived for the last two months, was what suited him best: Six eggs, 50 grammes nutrose, 200 grammes freshly pressed meat-juice, 400 c.c. thin broth, and 500 c.c. milk. In view of the patient's mental state I made no change in his diet, which contained 18 to 19 grammes of protein nitrogen, and had a heat-value of about 950 calories, and he took it for twelve days. Unfortunately no investigations of the urine passed during this period are available. At the end of this time the man said he must now fast for four days, as he had for years been accustomed to do from time to time. During these four days he drank only water and lemon-juice to the extent of about 1 litre a day; the urine contained 22·5, 26·4, 19·8, and 20·3 grammes nitrogen, and the body-weight fell from 53·6 to 52·8 kilogrammes. After this period the diet was rearranged and enriched; the weight increased, and the subjective discomforts were relieved. But the nitrogen excretion of this period remains unknown, as the patient was suspicious, and threw away his urine when he discovered that it was to be investigated.

This example shows clearly that chronic malnutrition is not characterized by a small nitrogen excretion; the output of nitrogen depends essentially upon the preceding diet. Except in cases of diabetes mellitus, and in persons undergoing "obesity" cures, it will usually be found that they who eat less than they require limit their consumption of protein as well as their consumption of non-nitrogenous foods.

In chronic malnutrition one usually finds but little urinary nitrogen, for it is often reduced to 5 to 6 grammes a day, and in earlier times this led to the supposition of the so-called "slowing of the metabolism." Properly interpreted, this phenomenon depends on two factors—(1) the poverty of the diet in protein, and (2) the tendency of the ill-fed,

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protein-starved body to economize its protein, and to retain material for the improvement of its juices and protoplasm from such protein as it does get whenever it can. Even when the supply of protein is minute, and the heat value of the diet is so small that there is a positive deficit of calories, this tendency to regeneration is capable of bringing about retention of nitrogen (see above the examples quoted from Fr. Müller, G. Klemperer, and v. Noorden). But this favourable result is not the rule, a positive nitrogen balance in malnutrition being associated with certain definite conditions.

It has repeatedly been found that animals dying of starvation show a new and often considerable increase in their nitrogen excretion usually just before death occurs. C. Voit (45) and his school connect this ante-mortem increase in the protein decomposition with the final disappearance of the disposable fat from the body. But recently Fr. N. Schulz (45) has attributed it rather to the death of a portion of the cells, preceding the death from starvation of the organism as a whole; the protoplasm of these dead cells is then consumed by the other cells that are still alive. But this view can hardly be maintained, as Schulz now seems to admit. It demands at the outset that dead cells should be found in the starving body towards the end, and modern histological technique would have no difficulty in demonstrating them if they really were present.

In opposition to Schulz's work, the earlier views are again upheld, and have been substantiated anew by the extensive researches of Voit's school [M. Kaufmann (46), E. Voit (47)]. Still, N. Schulz has done good service by reopening the old question, and the recent work of E. Voit and of N. Schulz has further shown that one of the causes for the terminal increase in the nitrogen excretion is the exhaustion of the reserve of fat. This exhaustion is of itself enough to account for the terminal and often sudden increase in the nitrogen excretion, which may, however, also be occasioned by other causes. It may be, for example, that starvation leads to the incomplete destruction or elimination of the poisons generated in the body itself, and that these poisons may give rise to a toxic decomposition of its protein. This terminal increase does not of necessity stand in direct relation with death by starvation, for it equally results from serious interference with the nutrition of various important organs [E. Voit (47)]. At this point the matter may be left, as it is not yet applicable to the metabolism of human beings.

(*b*) *In Chronic Malnutrition.*

The question of the decomposition of protein in chronic malnutrition, apart from actual starvation, has been already discussed. The dangers to which the protein of the body is always exposed when the heat value of the food taken is insufficient are dealt with in the physiological section. As is there shown—notwithstanding F. Hirschfeld's opposing views—the loss of nitrogen is not a direct and necessary consequence of inadequate heat-supply; reference may be made to the experiments upon convalescents in the next chapter, and to the cures for fatness (see the chapter

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on Obesity). Theoretically, however, such a loss is quite possible, since upon a diet inadequate in all of its constituents the organism economizes the valuable protein more and more, till finally it yields up none of its own protein to make good the deficient heat-supply, but meets the deficiency by the combustion of its reserves of fat instead.

This is clearly proved by experiments made upon a dog weighing 20 kilogrammes by E. Voit and A. Korkunoff (49). The dog was fed for a long time exclusively upon an insufficient meat diet, and lost 5·75 grammes nitrogen and 830 grammes of fat from its own tissues. It was next given a somewhat larger, but still insufficient, meat diet, and then not only established nitrogen equilibrium, but even put on protein, although at the same time it lost a further 730 grammes from its reserve of fat in the course of thirteen days.

Two similar experiments are recorded by Fr. N. Schulz (50); in one of them, on a diet rich in protein, the tissue protein remained almost intact, while the body-fat was used up. These experiments upon animals might have led to the conclusion that the nitrogen balance in malnutrition would be at its best when the diet was preponderatingly nitrogenous, and, as a matter of fact, this was the view generally held in the early days of the science of metabolism. In recent years, too, the belief has cropped up again more than once [D. Finkler[1] (51)].

But in man the case is quite different. A large diet of protein after a time does not protect the proteins of the body unless it be supplemented by an adequate diet of nitrogen-free foods. Precise observations and analytical figures dealing with diets rich in protein, but low in heat value, are not available. We do not, however, miss them, for simple clinical experience forms a sufficient guide. It is well known that underfed persons become poor in fat, poor in muscle, and poor in strength, and that a diet rich in protein cannot prevent their loss of power. Instructive examples of this can be drawn from experience of patients with gastric disorders. It is not so long ago that gastric hyperacidity was treated by administering a diet very rich in protein. This treatment in actual practice often took the form of a diet composed almost exclusively of meat, though such was not the intention of its first advocates [Riegel (52), and others]. On this diet the patients often fared very badly without obtaining relief from their hyperacidity; they lost not only fat, but muscle also.

I very early recognised the error of dietetic treatment on these lines and combated it. The exact figures for the nutritive values and protein-contents of the diets prescribed by medical men for the use of a number of patients during long periods are of interest in this connection. A feature common to all these cases was the considerable loss in weight, in muscle, and in capacity for work exhibited by the patients on these diets. In none of them was there the smallest difficulty in restoring the previous condition of good nutrition, of the muscles, and of the muscular power,

[1] The evidence adduced by Finkler is quite inadequate, and does not justify the conclusions he draws from it. To decide whether it was the protein that improved the state of nutrition in his cases it would be necessary to know—at any rate, approximately—the quantity and nature of his nitrogen-free diet. On this point, however, his communication says nothing at all.

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when the diet had been corrected by reduction of the protein and the free addition of fat.

Occupation.	*Age.*	*Approximate*		*Duration of Diet in Weeks.*	*Weight in Kg.*—	
		Protein per Day.	Calories per Kg. per Day.		Before.	After.
		Gm.				
Thatcher ..	32	120–140	23	6	58	52
Judge ..	35	130–150	21	5	55	51
Assessor ..	29	120–140	26	5	60	55
Merchant ..	41	140–160	26	4	53	50
Librarian ..	50	120–140	30	8	65	59

A characteristic example may be cited. In the summer of 1895 I was consulted by a judge, aged forty, who suffered from marked gastric hyperacidity. After a test-meal the HCl was 0·41 per cent., while his muscular power and nutrition were satisfactory. A summer holiday in the Black Forest brought much improvement, the patient gaining 3·5 kilogrammes and weighing 58 kilogrammes. The gastric contents were then examined twice, and the HCl was found to have diminished to 0·33 per cent. and 0·30 per cent. I then lost sight of the patient until January, 1896, when he came to me in a deplorable condition. He was much emaciated, and his previously powerful musculature was considerably shrunken. He stated that he had felt quite well until the end of November, 1895, when the gastric troubles began afresh; he went to a foreign clinique, and after being kept under observation for several days, was given an exact dietary to follow. To this prescription he had adhered with scrupulous accuracy for seven weeks; the gastric symptoms were certainly much improved, but the patient felt so weak that he came to ask if it was safe to continue the treatment. The diet to which he had kept for seven weeks ran as follows:

Morning: A small cup of tea, a thin slice of toasted white bread, the mince from 200 grammes of raw meat as free from fat as possible.—10 a.m.: two eggs.

Dinner: Plenty of meat (at least 200 grammes after cooking), one tablespoonful of potato *purée*, one small piece of toasted white bread, and one tablespoonful of strained vegetables.

5 p.m.: Tea and two eggs.

Evening: The morning meal repeated.—9 p.m.: ¼ litre milk.

On this diet, containing at least 175 grammes protein a day, and of low heat value, the body-weight fell from 57 to 52·5 kilogrammes in seven weeks, while the fat and also a large amount of muscle protein had disappeared.

Similar examples could be added to these, which prove sufficiently well that in heat-value starvation a protein-rich diet does not protect the tissue protein from being consumed.

In a large number of cases of chronic malnutrition the diet is less one-sided, and, as a rule, each of the chief classes of food-stuffs is equally deficient. Exact information is much to be desired as to the precise

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extent and period of the melting down of the body-protein through long spaces of time, and as to its quantitative relation to the maximum deficiency of heat value in the diet. Little is known on these points, since attention is generally paid only to high degrees of emaciation, or to the early stages of malnutrition [consult the researches of F. Hirschfeld (48), V. O. Sivèn (59), etc.]. Still, the series of researches by R. O. Neumann, G. Renvall, Clopatt, and Rosemann, do something to fill up the gaps (see Magnus-Levy, "Underfeeding," physiological section). These results are not free from contradictions, and show that in some cases where the heat value of the food is inadequate the body-protein remains untouched, while in others it is consumed although the nutritive conditions appear to be identical or even better.

As clinical observations are of greater practical interest, a few illustrative figures may be here inserted. I began these researches on the need for food during illness in January, 1893, but was forced to relinquish them up for extraneous reasons. They are given in detail because they indicate the path along which these practically and theoretically interesting questions may advance further. They deal exclusively with female patients who were admitted to the hospital in a state of lowered nutrition, either on account of slight nervous or rheumatic disorders, or of marked anæmia and general debility. These women all took their food badly, and in quantities that did not suffice to supply the heat they required. They were first kept under observation for a time—a week or two—on the diet to which they were accustomed. Then they were placed upon a diet (the nitrogen-content and heat value of which could be determined with ease) that was both very simple and also exactly the equivalent of the food to which they had previously been accustomed; milk, white bread, minced meat, and butter were chosen for the sake of simplicity. The quantity of this diet was increased every eighth day in order to determine the point at which progressive putting on of nitrogen and of weight took place.

The fæcal nitrogen was estimated at 1·0 gramme per day in these researches (see table, p. 17).

In these experiments a permanent increase in weight did not occur until an intake of 30 to 32 calories per kilogramme was reached. Hence these figures exhibit only a certain degree of regularity in the ratio of the caloric intake and the body-weight. The extent of the deficiency in calories does not here determine whether the nitrogen balance is positive or negative, for the nitrogen excreted in different cases showed wide variations when the heat-deficits were almost equal.

It should be noticed that in spite of the relatively small deficiency in the heat-supply the nitrogen excretion is occasionally very large (see the fifth case, p. 17). This appears to contradict what has been previously stated. Earlier in this chapter it was recorded, among the phenomena of convalescence or regeneration, that when the body is reduced by fasting, malnutrition, or disease, and has suffered loss of protein, it fixes greedily upon the protein of the food; it was described how this could take place when the heat value of the food was far smaller than it is in the cases recorded above. The apparent contradictions disappear, however, when

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it is remembered that in underfeeding a distinct putting on of nitrogen only occurs when the body is passing from a large deficit of heat to a smaller one; such a condition of affairs is well marked in the cases given below:

Age.	*Week.*	*Weight.*	*Albumin.*	*Calories.*	*Calories per Kg.*	*Nitrogen Retention or Loss (Average per Day).*
		Kg.	Gm.			Gm.
22	1	45·0	102	980	22	−2·3
	2	45·0	102	1,080	24	−1·8
	3	44·0	102	1,150	26	−0·3
	4	46·0	102	1,450	32	+1·5
	5	48·0	102	1,600	33	+2·3
21	1	50·0	95	900	18	−0·4
	2	49·0	95	900	19	−1·2
	3	48·5	95	1,050	22	−0·6
	4	48·5	95	1,300	27	+0·2
	5	50·0	95	1,550	31	+1·9
	6	53·0	95	1,900	36	+2·4
27	1	40·0	80	720	18	−2·8
	2	38·0	80	720	20	−2·6
	3	37·2	80	940	28	+1·5
	4	38·5	80	1,050	27	+1·9
	5	41·0	80	1,450	35	+3·3
28	1	48·5	80	1,300	27	−1·5
	2	48·5	80	1,300	27	−1·2
	3	48·0	80	1,300	28	−1·4
	4	49·0	80	1,400	29	−0·6
	5	50·0	80	1,500	30	+0·6
	6	51·5	80	1,900	37	+3·4
35	1	50·0	80	800	16	−1·9
	2	49·0	120	960	20	+0·4
	3	48·0	120	960	20	−0·9
	4	47·5	150	1,100	23	+0·9
	5	47·5	150	1,100	23	−0·6
	6	48·0	150	1,400	29	+0·8
	7	50·0	150	1,700	34	+2·9
	8	53·0	150	2,500	49	+4·2

Our present knowledge of the decomposition of protein in chronic underfeeding may be given in the following résumé:

1. After prolonged malnutrition the decomposition of protein is generally lessened; more of the tissue protein is lost in the earlier than in the later stages [F. Hirschfeld (48), W. Caspari (54), Sivèn (53), Neumann (55), E. Voit and Korkunoff (49), Fr. N. Schulz (50), and others]. Analogous are cases where the demand for heat is met fully, while only the protein intake fails to reach the required level [C. von Voit (56), Rumpf (57), Albu (58), Sivèn (53), Neumann (55)]. Loss of the body-protein does not necessarily follow in such cases. Nitrogen equilibrium can be maintained upon a protein decomposition far smaller than that which usually obtains—as, for instance, on a daily excretion of from 6 to 10 grammes of nitrogen in the urine and fæces. But usually it is only weakly persons who illustrate this possibility, and the question

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may properly be asked whether a larger protein intake would not bring them more nearly to their optimum of nutrition and strength.

2. Long-continued underfeeding, apart, perhaps, from minute and hitherto unproven degrees of caloric deficiency, invariably leads to loss of body-fat as well as to loss of tissue-protein, whether the supply of food protein is large or small. Only the absolute extent of nitrogen excreted varies with the latter factor; the establishment of a nitrogen balance is independent of its duration. A diet of low heat value but rich in protein can diminish, or even for a time postpone, the loss of nitrogen, but in the long run the result for human beings will be the same as if all of the components of the diet were diminished. If the heat value of the food be continuously inadequate, an increase of the protein taken will perhaps put a stop to the loss of nitrogen from the body for the time being, but—in man, at any rate—a moment comes when further increase of the food protein in the diet becomes impracticable. Under these circumstances the tissue-protein can only be maintained by adding nitrogen-free constituents to the diet in order to satisfy the demand for heat (see the fifth case above).

3. At present no exact quantitative measurements of the relations between the calorific deficit and the loss of body-protein in chronic underfeeding are extant. The loss is unexpectedly small in some cases, in others surprisingly large.

4. Whenever a poorly-nourished individual receives an increased amount of food, so that the deficiency of heat is decreased, an effort is made to retain nitrogen and repair the loss of cellular material that has occurred. This retention of nitrogen goes on until the body has readjusted itself to its new conditions of nutrition. Then the loss of nitrogen begins anew unless the calories required have been adequately supplied.

The question has recently arisen whether the molecule of the body-protein, when it is consumed in starvation or malnutrition, is broken down piecemeal by the successive losses of groups of atoms, or as a whole. Fr. Kraus (47A) describes the former process as a "partial degeneration of the chemical type." In researches undertaken at Kraus's suggestion, F. Umber analyzed the protein of fasting and of well-nourished cats. He concluded that the ratio of nitrogen to calories remained unaltered in the protein molecule, but that the results might indicate a splitting off of amino-acids from it. But it was found later that his analytical methods were inadmissible, and Kraus himself no longer attaches any importance to Umber's results. F. Blumenthal states that in starvation the easily detached hexose groups are the first to go. He also found a diminution in the pentoses of the nucleo-proteides. But no confirmation of these results was obtained from the careful researches made by G. Embden and Mancini in my own laboratory; they took the precaution of making the organs of fasting dogs free (or very nearly free) from glycogen by extirpation of the pancreas, or by poisoning with phloridzin or strychnine. The liver and muscles of the animals were used for the pentose estimations (47A).

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3. Division of the Tissue Losses in Starvation between Protein and Fat.

Reviewing the decompositions of the tissues in general, and of protein in particular, that take place during starvation, it appears that drafts are made upon the potential energy stored in both protein and fat. The reserve of carbohydrate is so much reduced by a short period of fasting that it need no longer be considered quantitatively when the fast is ended. Only a very small part of the output of energy is due to the combustion of protein, the great part arising from that of fat. Comparison of the figures, considered with an eye to the particular circumstances of each case, further proves that fat people decompose relatively less protein than those who are thin. The following values were obtained from starving individuals:

Day of Fast.	*Calories converted.*	*Calories evolved—*		*Total Calories.*	*Percentage of Calories evolved—*		*Observer.*
		From Protein.	From Fat.		From Protein.	From Fat.	
1	32·1	319·8	1999·5	2319·0	13·5	86·5	Voit, Pettenkofer, and Ranke (59).
2	30	205·0	1897·2	2102·2	9·7	90·3	
1–4	29	329·8	1288·2	1618·0	20·5	79·5	Zuntz-Lehmann (1) on Cetti.
5, 6	28·4	267·3	1237·4	1504·7	17·5	82·5	
7, 8	31·74	258·7	1407·3	1662·0	15·4	84·6	
9, 10	29·3	261·1	1247·4	1508·5	17·3	82·7	
1–6	26·81	280·6	1269·8	1550·4	18·0	82·0	The same, on Breithaupt.
5, 6	22·8	262·6	1029·6	1292·2	20·3	79·7	
1	33·15	303·5	1916·9	2220·4	13·7	86·3	Tigerstedt (12).
2	32·0	320·5	1781·9	2102·4	15·2	84·8	
3	31·20	339·4	1684·7	2024·1	16·7	83·3	—
4	31·13	341·4	1651·9	1992·3	17·1	82·9	—
5	31·23	286·1	1684·7	1970·8	14·5	85·5	—

To the few results from experiments on human beings may be added those obtained from animals (60). Thus the cat found by Bidder and Schmidt to contain 40 grammes of fat after death evolved energy thus:

Day of Fast.	*Energy derived—*	
	From Protein.	From Fat.
1–6	47·5 per cent.	52·5 per cent.
7–12	38·3 ,,	61·7 ,,
13–18	33·5 ,,	66·5 ,,

Two dogs of Pettenkofer's gave the following numbers:

Day of Fast.	*Percentage of Energy evolved—*	
	From Protein.	From Fat.
I. 2	27·1	72·9
5	13·2	86·8
8	11·5	88·5
II. 6	13·3	86·7
10	8·6	91·4

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The longer the fast lasted the smaller was the protein decomposition. The protein was spared, the less valuable fat was sacrificed.

Although exact figures for the chronic underfeeding of both man and animals are lacking, it may be deduced that a deficiency in calories is made up at the expense of the fat and with all possible economy of protein, supposing that the natural conditions have not been previously modified by some arbitrary dietary. To illustrate this point I have completed the figures just given by the following table, where the figures for only the first week are set out :[1]

Case.	*Weight in Kg.*	*Calculated Calory Requirements.*	*Intake of Calories.*	*Nitrogen Excretion.*	*Deficit of Calories made up—*	
					From Protein (about).	From Fat (about).
					Per Cent.	Per Cent.
1	45	1,350	980	18·6	15·5	84·5
2	50	1,500	900	15·6	1·7	98·3
3	40	1,200	720	17·7	14·6	85·4
4	48	1,440	980	13·2	1·6	98·4
5	48·5	1,455	1,300	14·4	24·0	76·0
6	50	1,500	800	14·8	7·1	92·9

4. The Weight of the Body.

It is natural that a great fall in the weight of the body should result from the loss of protein, fat, water, and salts experienced by the body during starvation.

	Day of Fast.	*Loss of Weight.*	*Per Cent. of Original Weight.*	
		Kg.		
Cetti	10	6·35	11·14	
Breithaupt ..	6	3·62	6·0	
Succi	30	11·96	19·2	Three separate experiments, Luciani (16).
,, ...	30	14·3	22·7	
,, ...	30	13·1	21·4	
Fasting man ..	5	5·0	7·4	Johansson.

The development of correct relations between the water loss and the secretory functions is an important factor in the fight with hunger. The store of carbohydrates in the body is very small, and, with the exception of chitine, is easily utilized. Fat furnishes the chief source of energy during hunger, but it is by no means fully consumed, since in part —particularly as lecithin—it forms a definite constituent of protoplasm. Protein is disintegrated in a somewhat regular manner, the phosphorus-free albumin being decomposed during the first days, the phosphorus

[1] It is here assumed that the true conversion of energy of ill-fed, thin persons is at the rate of at least 30 calories per kilogramme per day. Should the rate be higher, then the number of calories made up by the combustion of fat will be greater, both relatively and absolutely ; 1 gramme nitrogen is calculated roundly at 25 calories.

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containing albumin thereafter. The pentose group of the nuclein is to a certain extent unchanged. The absolute loss of water, total energy, and albumin, sufficient to cause death, form fairly constant factors for each type of cell (Slowzoff, B., "Zur Pathologie des Hungers," *Mitth. d. Militärmed. Akad.*, Bd. XI., 1905; Delion, Soc. Biol., Bd. LVIII., p. 931, 1905).

The loss of weight follows a steep parabolic curve, as shown by Luciani (61), and is more rapid at first than later. The total loss is relatively small, because the subjects of these experiments all drank small quantities of water. For large amounts of water the fasting man has no desire. The significance of this consumption of water is illustrated by the paradoxical increase of weight [Tuczek (62)] exhibited by men who drink water during fasting, particularly during short periods. This, of course, depends upon a temporary retention of the fluid.

It is commonly calculated that death occurs from acute starvation when from one-third to one-half of the weight has been lost. So far as concerns man, however, such figures are mere guess-work; exact determinations of this point are, perhaps fortunately, still to seek. In the same way the time necessary to starve a man to death is unknown. Succi's repeated thirty-day fasts (at Paris, Milan, and Florence) can be guaranteed; the forty- and fifty-day fasts of Merlatti and Tanner are less trustworthy. In dogs death occurs in from fourteen to sixty days, according to their age and fatness; newly-born animals die sooner—in about three days. The loss of the original weight on death by starvation was 48·1 and 48·9 per cent. in two full-grown dogs of Falck's (63), 44·19 and 48·53 per cent. in two dogs of Luciani's (64).

Similar losses of weight in man are only observed when the progressive wasting is retarded to a certain—though ever so minute—degree by the taking of food. The extent to which loss of tissue can proceed, and the degree of emaciation that can be tolerated for long periods, is really surprising. Attention may be drawn to two cases mentioned already: the first, a girl with œsophageal stricture, whose weight fell in six and a half weeks from 45·5 to 35·0 kilogrammes, a loss of 27·5 per cent. of her original weight; the second, a young woman with gastric ulcer, who lost 31·2 per cent. of her original weight in five to six weeks (51 to 35 kilogrammes). Liebermeister (65) records cases where the loss of weight amounted to nearly half the weight at the outset. I myself treated a man, aged twenty-four, with pyloric stenosis and gastrectasis, whose weight fell from 161 to 82 pounds in less than two years (49 per cent.), yet he could still perform much mental and a certain amount of light physical work.

Rubner's (66) calculations as to the loss during fasting of the potential energy stored in the body are of interest. At death this loss may amount to 70 per cent. The combustible material in a rabbit's body —excluding the skin—had the heat value of 2,682·1 calories. Death occurred on the nineteenth day of starvation, and the animal had then decomposed protein and fat to the value of 1783·99 calories, only 29·76 per cent. of its heat value remaining unused. Thus the daily consumption of the potential energy originally present in the body was 3·69 per cent.

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This loss of weight falls very unequally on the different organs. The fatty tissue is chiefly affected—about 95 per cent. disappears. The muscles, glands, and blood come next, losing from 40 to 50 per cent. to supply the protein consumed during the fast. The different forms of protein waste unequally. In the case of mice, C. M. Nemser (67) found that the nuclein fares better in starvation than the other tissue protein. This observation is confirmed by the microscope, which shows that the cell body is much more reduced by the atrophy of inanition than the nuclei of the cells are [Miescher, Morpurgo (68)]. The bones waste less than the tissues that are rich in protein ; only 10 to 15 per cent. of their weight has been lost when death occurs. The tissues of the central nervous system remain practically unchanged. Edlefsen (55) claimed as an exception to this statement that nervous tissue loses lecithin in starvation, but recent investigations [Herter (69)] do not confirm his view.

Comparison of the figures obtained from pigeons, rats, rabbits, dogs, etc., show that the wasting of the various organs does not take place in the same proportions in different kinds of animals. K. Tominaga (70) has proved the same thing for the loss of nitrogen from the various organs.

For details as to the shrinking of the organs in starvation, and for the literature, reference may be made to the comprehensive works of A. K. Sedlmair and E. Voit (71).

5. Influence of Starvation on the Organs of Digestion.

Since there is no call upon the digestive organs during starvation their activity is lowered, although not uniformly.

1. *The Secretion of Saliva* diminishes in acute starvation even when water is taken *ad libitum*. Thus Succi, on the seventh day of his fast, only produced as much saliva by the movements of his jaws in three hours as under ordinary circumstances is secreted in five minutes. Should water be withheld as well as food, then the secretion of saliva lessens still more rapidly, as every-day clinical experience shows.

The diastatic ferment in the saliva collected during Succi's fast was subnormal in quantity, and since the amount of the saliva was lessened, the total ferment was decreased. In the case of Breithaupt, on the other hand, who secreted very little diastase by the kidneys before the fast began, Leo (73) found more and more of the ferment in the urine day by day, till finally the amount was far in excess of that present under normal circumstances. This diastase is only partially derived from the salivary glands, the rest coming from the pancreas. Grützner (74) says that " starving persons absorb the salivary glands as well as their contents." It may be added that one regularly finds large amounts of the active ferment in the morning urine of many people when they have not taken any food for from twelve to sixteen hours [Leo (73)].

But even after protracted starvation, and with patients in the worst possible state of nutrition, the saliva does not lose its diastase completely. Without making many quantitative experiments I have never

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failed to find a marked amylolytic power in the saliva of a large number of persons reduced to a very low state by want of nourishment. Quantitative examinations have been made in two cases, the first being that of a man with gastric disease, the other that of a hysterical young woman who had become very thin from weeks of uncontrollable vomiting, and could only retain very small amounts of food—about 400 c.c. of milk a day. In each case the saliva (about 10 c.c.) was collected during a fast; it only converted about half as much starch as a sample collected later when the nutrition had improved. The further observation was then also made that the salivary sulphocyanide is much diminished in malnutrition. But later experience has shown that this result is not constant in either chronic or acute starvation. Four cases of gastric ulcer were treated by the withdrawal of all food. In three of them the sulphocyanide reaction increased distinctly after the first day of fasting, almost disappearing on the third day, while in the fourth patient the strength of the reaction remained almost unchanged to the end of the third day of the fast. The saliva secreted by such patients when they chew india-rubber has a distinctly acid reaction; such acidity is often found in the saliva of healthy persons who have taken no food for several hours [G. Sticker (75)].

2. *The Gastric Juice.*—Physiologists are familiar with the close connection that exists between the secretion of gastric juice and the stimulation of the stomach by food. While the stomach is empty the secretion is commonly very small, if, indeed, it is not absolutely *nil* [J. Schreiber, A. Huber, H. Rosin, E. Pick, F. Martius, and A. Schüle (76)]. In protracted fasting the quantities of pepsin and HCl secreted are barely worth mentioning. This fact is *a priori* probable, and receives support from the experiments upon Succi (13). Succi was able at will to vomit water recently taken without having recourse to the stimulus of a sound or bougie—a matter of some importance. Daily examination of the fluid thus voluntarily vomited showed epithelial cells and mucus; acid was never present, and pepsin was there in traces only. But he still retained the power—at any rate, some days after the fast began—of secreting HCl and pepsin in response to the physiological stimulation of food. A case of my own illustrated the same fact. A patient with melancholia refused food and drink for three and a half days; the first food she took consisted of a cup of milk and two rusks. Three-quarters of an hour later the gastric contents were returned, and contained normal amounts of acid, peptone, and HCl [von Noorden (77)].

On the other hand, deficient HCl secretion can often be demonstrated in persons who have become very ill from continued underfeeding. The HCl is not wholly absent, but it is not secreted in such quantity as to oversaturate the food taken, as it is in health. Hence it is that most books dealing with diseases of the stomach very properly describe conditions of prolonged inanition and general bodily wasting among the causes of diminution of the secretion of HCl. Contrariwise, all the evidence goes to prove that the secretion of pepsin can be well maintained up to the later stages of bodily disintegration.

Malnutrition leading to extreme loss of body-weight does not in-

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variably put a stop to the production of HCl. One often sees persons with nervous dyspepsia who are very much emaciated, yet continue to show hyperchlorhydria; such cases may be most successfully cured by systematic dieting [von Noorden (77A)].

Like diastase, pepsin or its zymogen is absorbed, and is secreted in an active condition in the urine. Doubts have been expressed as to whether the pepsin in the urine really is derived from the glands of the stomach [Salkowski (78)]. But its gastric origin is made more probable by the investigations of M. Matthes (79), who found no pepsin at all in the urine of dogs after extirpation of the stomach. Grober (79A) has arrived at the same conclusion by different methods. Pepsin, like diastase, is found freely in the urine passed in the early morning hours, or at the height of the physiological pause in nutrition [W. Sahli, Gehrig, H. Hoffmann, Leo, R. Neumeister (80)]. If the fast continues, the urinary pepsin increases for several days [Grützner (74) for the dog and Grober (79A) for man]; later, it diminishes rapidly [Schnapauff (81), Luciani (13)]. Merzbecher (81A) showed that large quantities of propepsin accumulate in the gastric mucosa of hibernating animals during their long fast.

No experiments on the behaviour of rennin during starvation are extant; Senator (82) did not find trypsin in the urine of Cetti and Breithaupt.

3. *The Liver and Bile.*—The secretion of bile by fasting animals has often been studied. It is less during starvation than when the diet is full, decreases progressively from the first day of the fast, but is never completely absent [H. Nasse, F. Bidder and C. Schmidt, A. Kunkel, K. Spiro, A. Vossius, Lukjanow, Stadelmann, P. Albertoni, and Willishanin (83)]. As an example, E. Stadelmann's experiment on a dog weighing 12½ kilogrammes may be cited; it secreted 282 c.c. of bile during the last day on which it was fed, but during the next five periods of twelve hours only 72·0, 71·5, 62·5, and 54·0 c.c. During five days' fasting the bile secreted by a dog of Spiro's diminished from 38·5 to 20·0 c.c.

The bile secreted by a fasting man cannot, of course, be measured. The figures found after operation for gall-stones are not as uniform as they should be. That bile is still secreted during fasting was suggested by Gerhardt's observation that the gall-bladder may be palpable and tense when no food is being taken.

The quantity of the bile secreted during starvation is diminished, but its concentration usually increases; yet the daily residue left on evaporation is less than the normal [Bidder and Schmidt, Stadelmann, Lukjanow, Willishanin, etc.].

Information as to the production of bile-pigment and its passage into the intestine of fasting persons can best be obtained from the hydrobilirubin; Fr. Müller (84) found an average of 15·34 milligrammes in the daily urine of four healthy persons on full diet. D. Gerhardt (85) observed 11·06 milligrammes, on an average, in the urine of the first five days of fasting. Daiber (86) gave analogous values in the case of Succi. The figures do not differ much from the normal, and Fr. Müller

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(13) showed that the scanty fæces were similarly rich in hydrobilirubin during fasting. Even when there is marked emaciation, in consequence of long-continued underfeeding, the urine still contains hydrobilirubin. The daily quantities present in the urine and fæces of the hysterical girl with hyperemesis mentioned above were 0·11 and 0·31 gramme respectively; both values were smaller—0·08 and 0·27 gramme—afterwards, when she had attained a state of good nutrition. The maintenance of this excretion of hydrobilirubin during fasting is quite intelligible from a biological point of view, for the pigment results from the reduction of the bilirubin in the intestine [Fr. Müller (88)]. It is excreted as the refuse of the hæmoglobin which the organism continues to break down even during starvation.

The glycogen in the liver is consumed rapidly at first, but more slowly as the fasting continues. This fact is of importance in connection with the experimental investigation of the formation of carbohydrate in the animal body. Very various kinds of food have been given to animals after long periods of starvation, and from the amounts of glycogen found in the liver after such feeding conclusions have been drawn as to the capacity or incapacity of the food to subserve the formation of glycogen. We have seen that even in advanced degrees of starvation the liver habitually contains only a small amount of glycogen. But under certain circumstances the amount may be very considerable—at all events, too great to be neglected—and Pflüger (88A) has very rightly drawn attention to this fact again. Before it was properly understood the fact was surprising; it is no longer so now that experiments in the respiration chamber have made it probable, and chemical analyses have proved that glycogen is formed anew and stored up even during fasting [Lehmann-Zuntz (89), Vogelius (90), J. Frentzel (91)].

Little is known concerning other changes in the functions of the liver in starvation. Pflüger and Schöndorff (90) demonstrated that the perfusion of normal blood through that organ while still alive produced less urea if the animal from which it had been taken was fasting than if it had been well fed. It remains uncertain, however, whether the cause of this phenomenon lies in a diminution of the synthesizing power or the number of the liver cells, or in a lack of the ferment or of one of the components essential to the synthesis. A similar interpretation must be placed upon the fact, noted by Pugliese (91), that when an animal is given phenol after a long fast it produces much less phenyl-sulphuric acid than a normal animal does. Pugliese's researches do not make it certain whether this depends upon a diminished action of the liver—in which organ the combination between phenol and acid takes place—or not. If the experiments are repeated, care should be taken to see that the phenol does not appear in the urine combined with glycuronic in place of sulphuric acid.

4. *The Intestinal Secretions and Fæces.*—The excretion of the intestinal secretions in starvation cannot be discussed apart from that of the fæces. The latter include not only the residuum of the intestinal juices, but also the unabsorbed constituents of the bile and the débris of shed epithelium. The residue left by the bile is very small, for most of it is reabsorbed

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before it reaches the large intestine [Fr. Voit (92)]. The bacteria, on the other hand, chiefly determine the quantity and composition of the fæces in starvation [Schmidt and Strasburger (93)]. Fr. Müller (1) found that during starvation the fæces contained hardly any soluble albumin, but a relatively large proportion of nuclein.

Such fæces are described by Fr. Müller (94) as "formed, yellowish-brown, uniform masses, of average consistence, and similar in appearance to the fæces passed when the diet is mainly composed of meat." Their reaction is feebly acid. Müller records that the daily quantity of dried substance amounts to 18 to 23 grammes; in five cases the daily nitrogen was 0·316, 0·116, 0·446, 0·223, and 0·170 gramme, an average of 0·254 gramme. The variations are wide, and correspond with the fact that, on full diet also, the composition of the food is not the only factor determining the quantity of nitrogen in the fæces, for considerable individual variations have to be reckoned with [von Noorden (95)].

The excretion of fat, which amounts to 1·21, 0·57, and 1·14 grammes a day is a matter of importance. About one-half consisted of neutral fats and cholesterin, the other half being composed of free fatty acids and soaps. It is remarkable that the starving organism did not avail itself again of these relatively large amounts of fat, which obviously are derived from the glands.

In connection with the evacuation of the fæces in starvation the following question is one of importance for the dietetic treatment of the condition: Does the absorbing power of the intestine diminish in consequence of long-continued malnutrition? The answer is in the negative. Fr. Müller (96), for example, in the case of his emaciated patient with stricture of the œsophagus, found 0·791 and 0·57 gramme nitrogen in the fæces while the diet consisted of milk and eggs. Klemperer (97) found 0·48 gramme nitrogen in a smiliar case that was fed on milk, eggs, and white bread. I myself (98) found that the fæcal nitrogen and fat, calculated on the dried substance, corresponded with the nature and quantity of the food taken by a patient with gastric troubles. In later researches I gave more fat freely in the diet, and often found that it was absorbed uncommonly well by patients who had been previously underfed, even when the large supply was still further increased. Thus, when the hysterical patient with hyperemesis, who has been mentioned so often, took to a diet of milk, cream, eggs, white bread, and butter, the vomiting suddenly ceased. This diet contained 18 grammes of nitrogen and 200 grammes of fat; the patient excreted an average of only 1·0 gramme of nitrogen and 4·2 grammes of ether extractives in the fæces of the first three days. Another female patient, whose weight fell from 51 to 42·8 kilogrammes during a three weeks' gastric crisis, excreted an average of only 3·9 grammes of fat in the fæces passed from the third to the eighth day after the crisis was over; her food at this time contained at least 250 grammes of fat per diem. Similar observations on the influence of a period of acute starvation have been published by W. Sokolow (99) and Johansson (100). Immediately after the fast food appears to be absorbed distinctly better than before it.

5. *Intestinal Putrefaction.*—When no food is taken, no protein reaches

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the intestine to undergo putrefaction. So it might be anticipated that the aromatic bodies and the sulphuric acid esters that are characteristic of the putrefaction of protein would disappear from the urine in inanition, or at least diminish greatly in quantity. This, however, is not the case—or, rather, is not always the case—nor does it apply equally to all the products of the putrefaction of protein. There are important differences between the accounts given by different observers.

The indigo-forming substance in the urine generally lessens apace [Tuczek (41), H. Senator (101), Fr. Müller (1)], though in other instances it remains quite high during a long period of starvation [E. and O. Freund (226), recording two peculiar observations made on women during the first five days of fasting]. The excretion of phenol rose considerably (102) in the case of Cetti—that artist in starvation—and reached the enormous values of 137 and 155 milligrammes on the eighth and ninth days of his fast; before the fast began the value was 16·6 milligrammes. The behaviour of the sulphuric acid esters was different, as the following table shows:

Cetti ..	..	mean of 1st	to 6th days	..	0·094	gramme H_2SO_4	esters.
„	..	„ 7th	„ 10th „	..	0·270	„	„
Breithaupt	..	„ 1st	„ 6th „	..	0·266	„	„
Succi, I. (13)	..	„ 5th	„ 29th „	..	0·076	„	„
„ II. (26)	..	„ 1st	„ 20th „	..	0·138	„	„

These variations do not conceal the fact that putrefactive products are still formed in the intestine during starvation; they are derived from the nitrogenous intestinal secretions and the epithelial detritus. According as one or other type of bacteria flourishes or disappears, more indol and skatol are formed in one case, more phenol and aromatic oxy-acids in another. The action of the bowels also influences the quantity of these products; for, as J. Munk (103) remarks, prolonged retention of the intestinal contents promotes both the formation and the resorption of putrefactive products.

In earlier days different conclusions used to be drawn from the continued elimination of aromatic decomposition products in starvation. The indol, phenol, etc., were supposed to be derived from the breaking up of the tissue-proteins, and this old view still crops up again from time to time [O. Rosenbach, F. Blumenthal, C. Lewin, F. Rosenfeld (104)]. But the recent evidence adduced in its favour is no sounder than the old [Allinger, Scholz, M. Gentzen, and others (105)]; the hypothesis rests on an unsteady basis, because it has been proved that putrefiable materials are still present in the intestines of fasting persons. Even the absolute increase of the aromatic compounds in the urine that is sometimes seen does not argue in favour of other sources for them besides the intestine, because pathological processes such as hæmorrhages often occur there during fasting, and so naturally give the bacteria of putrefaction a fresh supply of material on which to work [Ortweiler (106)]. (Compare here Magnus-Levy's section on Aromatic Compounds in the physiological section of this book.)

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6. The Influence of Starvation and Underfeeding on the Blood.

(a) Concentration, Red Blood-Corpuscles, Hæmoglobin, and Protein-Content.

1. *During Complete Abstinence.*—Panum's (107) numerous systematic determinations and his critical sifting of the rich material in the older literature showed that the percentages of solids and corpuscular elements in the blood were but little deranged by fasting. The blood "atrophies," and its most important constituents diminish in proportion to the diminishing body-weight.

This is also attested by the careful comparative investigations undertaken by Voit (108) and by Sedlmair (71). Any changes that take place are in the direction of slight inspissation: the water decreases relatively, while there is a relative increase in the residue on drying, in the specific gravity, in the hæmoglobin, and in the blood-count [see the researches on animals by Panum, Subbotin, L. Hermann and Groll, H. Nasse, Magendie, C. von Voit, Popel, Poletaew, and E. Grawitz (109), and on man by Senator, Luciani, and Andreesen (110)].

The molecular concentration has been shown by Mayer and by Figari (III.) to remain unchanged; the latter found $\Delta = -0{\cdot}56°$ up to the fourteenth day of fasting.

The researches of A. E. Burckhardt, J. Levinski, Th. St. Githens on dogs, and S. Wallerstein on the rabbit, indicate that the globulin of the plasma increases relatively, while the albumin decreases (112). Burckhardt explains this by the supposition that the globulin of the plasma is derived more from the tissues, the albumin more from the food.

G. Gallerani (113) states that the resistance of the hæmoglobin, measured by Mosso's method, increases during fasting.

Little difference is made in the composition of the blood if fluids are withheld as well as food. But withdrawal of water alone from the diet, which is then given dry, does inspissate the blood considerably (up to 5 per cent.) [Th. Jürgensen, Leichtenstern, Reinert, Dennig, Straub, H. Salomon, and others (114)]. Under such conditions the molecular concentration appreciably increases. [A. Mayer (III.)] found the freezing-point lowered in a dog to $-0{\cdot}68°$ and $-0{\cdot}72°$, the normal lowering being from $-0{\cdot}57°$ to $-0{\cdot}61°$.

2. *The Effect of Chronic Underfeeding.*—This is commonly associated with disease, and so its influence is much harder to estimate. Changes in the constitution of the blood naturally cannot be put down to the diet if disease is present; but the objections to such a course are least in the cases of chronic gastric disease (excluding gastric hæmorrhage or carcinoma). The alterations in the metabolism of gastric disorders are mainly due to inanition (von Noorden (98)].

The hæmoglobin and blood-corpuscles have been found normal, or nearly so, in a number of cases of ulcer of the stomach [Häberlin, Oppenheimer, Fr. Müller, Schmaltz (115)]. In other cases they were distinctly diminished [Osterspey (116)], but hæmorrhage may have combined to produce this result in all the cases, for it certainly did so in some of them.

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I myself found the dried substance of the blood to be 21 to 22·5 per cent., and the corpuscular count to be normal in five cases of gastric ulcer in which emaciation but no hæmatemesis had occurred. Normal blood-counts and normal hæmoglobin values were also obtained from the blood of a number of men and women who had taken their food ill for long periods, and had lost much weight in consequence of nervous dyspepsia. Yet all these individuals gave so distinct an impression of marked anæmia that the normal percentages found for the composition of the blood caused some surprise. Reinert (117) found values for the density that lay near the upper limits of the normal in the case of an insane patient who had taken her food badly for many months and was much emaciated. Similar records have been made by Sahli, Laache, and Oppenheimer, who all remark that the hæmoglobin and blood cells of persons with very pale skins and mucous membranes may none the less show normal values (118). My own experience is that such people are mostly thin and ill fed; their condition should rather be spoken of as oligæmic than anæmic.

In prolonged malnutrition, therefore, the factors that produce an increase and a decrease in the specific gravity of the blood often balance one another, combining to produce blood of normal composition. But the first effect of underfeeding seems to be to diminish the concentration of the blood, and more particularly so that of the serum [E. Grawitz, A. Landau (119)]. A sparing diet of milk (1½ litres a day) diminished the amount of serum, albumin, and globulin in so short a time as a week [Landau], while the osmotic pressure remained unaltered.

	Nitrogen contained in the Serum.		
	Case 1.	Case 2.	Case 3.
	Per Cent.	Per Cent.	Per Cent.
Beforehand ..	1·428	1·344	1·386
After a week ..	1·370	1·316	1·370

Further information may be sought from experiments upon animals. H. Nasse (109) states that the specific gravity of the blood fell from 1057·5 to 1055·8 in a dog fed—without definite purpose—on a protein-poor but carbohydrate-rich diet. The difference here is very small; the experiments of von Hoesslin (120), which continued for months, are more convincing. Taking two dogs of the same litter, he fed one of them (A) very liberally, while the other (B) received only one-third as much food.

	Weight in Kg.		*Percentage of Hæmoglobin.*		*Red Blood Cells* (1 = 1,000,000).	
	A.	B.	A.	B.	A.	B.
After 56 days ..	11·6	5·5	10·2	11·2	—	—
,, 124 ,, ..	23·4	8·5	14·9	16·0	6·82	7·97
,, 1½ years ..	30·3	9·5	17·6	15·5	8·3	7·3

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Four parallel researches where the diets were rich or poor in protein led to similar results. Von Hoesslin states that chronic underfeeding influences the total volume of the blood, as well as the mass of all the tissues, and produces individuals who are poorly supplied with blood, fat and muscle. But he adds that the common view to the effect that the blood of such persons is always watery and poor in hæmoglobin and blood cells cannot be maintained; such a condition, if present, is due to the co-operation of other injurious forces. My own opinion is that von Hoesslin's view is right here, speaking practically, in contradistinction to the theoretically more important determinations of Grawitz and Landau. The opinions of P. Ehrlich and A. Lazarus (121) agree with von Hoesslin's.

In chronic malnutrition, then, the percentage of water in the blood is maintained approximately at the normal level. It appears to me that it is not definitely proved in the case of man that the tissues become richer in water, although certain authors [Munk (122), Schöndorff, Fr. N. Schulz (123)] have described such a condition in animals. One often finds that the tissues of badly-nourished persons are abnormally watery, or even œdematous. But in such cases malnutrition is conjoined with disease, and it is difficult to be sure how much should be ascribed to the influence of the one or of the other of these two factors.

It is many years since von Hoesslin (120) drew attention to this important fact: that increase of the weight of the body and the return from state of bad to a state of good nutrition lead to an immediate relative decrease in the hæmoglobin. This does not, of course, signify that a destruction of red cells or of hæmoglobin takes place; it only indicates that the volume of the body and the fluids of the blood are regenerated more rapidly than the red corpuscles. This phenomenon was observed (124) in the cases of Breithaupt and Cetti. Grawitz (125) states that this condition of dilution affects the blood-serum more than the blood as a whole when the starved body returns to a state of better nutrition, and that it may persist for a long time if the diet is not made fully adequate, and does not meet the body's demand for both nitrogenous and non-nitrogenous foods.

An admirable illustration of this is afforded by an unusual observation made in Gerhardt's clinique. A working woman, about thirty years of age, who had been very ill-nourished previously, was much emaciated by a gastric crisis and uncontrollable vomiting, which lasted three weeks. Immediately the crisis was over she was at once put on a very rich diet. While the weight of the body increased and convalescence progressed rapidly, the density of the blood fell 0·47 per cent., and that of the serum 0·82 per cent. Similar, though less complete, observations are recorded by Buntzen (126) and by Stierlin (127), to which von Hoesslin refers. In opposition, then, to the current views, diminution in the blood's specific gravity may sometimes be a sign of good semeiotic and prognostic import (see table p. 31).

The tissues also share in the rapid increase of fluid seen when fasting is over. Clinical opportunities often allow the observation of considerable augmentations of weight during the first few days of better nutrition

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	Body-weight in Kg.	Specific Gravity of—	
		The Blood.	The Serum.
During the inanition	48·3	1058·0	1029·0
Two days before it ended	45·9	1060·0	1030·5
Three days after the rich diet	47·2	1057·5	1028·0
Four days after the rich diet	48·9	1056·0	1026·0
,, ,, ,, ...	50·4	1055·0	1023·0
,, ,, ,, ...	52·1	1055·0	1022·0
,, ,, ,, ...	53·7	1055·0	1025·0
Eight days after the rich diet	56·1	1056·0	1027·5

after a period of partial or complete starvation. Such examples occur after an œsophageal stenosis has been relieved, or in cases of tramps who have been extremely ill-fed; such increases in weight cannot be assigned solely to the putting on of fat and protein. In numerous cases observed by myself the weight added during the first week has been three times as great as that which could be attributed, even under the most favourable conditions of nutrition, to the protein and fat added to the tissues of the body. In fact, even œdema may appear, although both heart and kidneys are sound. It must remain undecided whether this œdema is due to abnormal permeability of the capillary walls, or to injury done to the tissues by the preceding malnutrition.

(*b*) *The Leucocytes.*

During starvation the leucocytes are diminished in number. This is clearly shown by two experiments on Succi. Luciani (13) found in one of them that the leucocytes sank from 14,530 to 861 per c.mm. between the first and seventh day of the fast; they then remained for twelve days at about 1,000, increasing a little towards the end of the experiment. During the experiment at Vienna, where Succi fasted for thirty days, Tauszk (12) found:

Day of Fast.	*Red Cells.*	*White Cells.*
3	5,246,000	9,600
8	4,840,000	8,300
13	4,932,000	7,200
17	5,136,000	6,900
21	5,160,000	5,500
25	5,268,000	4,800
30	5,472,000	4,200

When food was again taken, the number of leucocytes increased rapidly—the leucocytosis of digestion [Senator (124)]. Further observations on this point are recorded by Lioubémoudroff and Monaco and Poletaew (130).

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Whether a marked decrease of white cells is characteristic of cases of chronic underfeeding is not certain, as almost all the persons hitherto examined were suffering from other diseases. Reinert (114) states that in three cases, which may fairly be used for our purpose, the numbers were almost normal. No distinct leucopenia was observed in Osterspey's (116) gastric cases, amongst whom were undoubtedly many underfed persons. In my clinique very low numbers of leucocytes (3,000 to 4,000) were frequently found in persons who, free from organic disease, were emaciated from underfeeding. As the nutrition improved the numbers were gradually doubled. (The examinations were always made under identical external conditions—hour of the day, etc.)

There is need for further research as to the type of white blood cells met with in inanition, especially with regard to the leucopenia.

(*c*) *Alkalinity.*

The alkalinity of the blood, as measured by its CO_2 content, remains unaltered during starvation. Geppert found that the normal average in arterial blood was 29 volumes per cent. of CO_2 with a diet of meat and fat; after four days of starvation, in four cases the volumes found were 30·26, 30·7, 32·6, and 30·0 per cent. In rats direct titration gave the same results. Drouin found the alkalinity in normally-nourished animals to be 100 c.c. of blood = 244·5 milligrammes NaOH, and, after prolonged starvation, in the proportion of 234·4 milligrammes NaOH. The difference is unimportant.

(*d*) *Amount of Fat.*

Fr. N. Schulz has observed that in starving dogs the fat in the blood increases—as much, indeed, as by 50 to 100 per cent. of its original quantity; according to L. Daddi (134), the blood of animals contains more that is soluble in ether during the first fourteen days of starvation, while later this diminishes again. The fat in the lymph increases more than it does in the blood [Boeniger (135)]—1·4 per cent. in the case of chronically underfed human beings, as compared with the normal 0·75 to 0·85 per cent. It should be borne in mind that in cases of starvation of whatever degree the tissue fat disappears. The fact that the blood is rich in fat is the visible expression of the transposition of fat from the reservoirs in which it is stored to the organs in which its decomposition is going on.

(*e*) *Amount of Sugar.*

Sugar does not disappear from the blood, even in cases of prolonged starvation. It is found in about the same quantities as with mixed diet [Cl. Bernard, Chauveau, von Mering, Otto, Seegen, and others (136)]; some analyses even give a somewhat larger amount in starvation, but these differences hardly exceed what must be allowed for experimental error.

The decrease of glycogen in the liver and muscles during starvation,

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on the one hand, and the presence of sugar in the blood on the other, supplied Seegen with the basis for his attacks on the theory of the formation of sugar from glycogen. He was mistaken, for this condition of affairs would also obtain if the glycogen existing in the liver were to be straightway carried away from that organ, in order to pass by way of the blood to the muscles and glands in need of sugar. The fact only proves that even during starvation sugar is constantly being formed, and this agrees with other statements already made.

The blood of a starving animal retains its normal percentage of sugar even under the severe demands for sugar which arise during "strychnine" convulsions. Whether under these conditions the carbohydrate leaves the liver as glycogen or as dextrose is not yet clear.

(*f*) *Amount of Ammonia.*

The statements that have been made as to the amount of ammonia in the blood during starvation are at variance with one another. Nencki, Pawlow, and Zaleski (137) found a considerable decrease (0·38 milligramme NH_3 in 100 c.c. of blood, compared to the normal 1·5 to 2·7 milligrammes). W. Horodynski (138) asserts that the amount of ammonia in the organs and also in the blood increases during starvation, and does so in proportion to the length of time it lasts. We await further investigations. *A priori*, Horodynski's observations seem highly probable, for in starvation large numbers of organic and inorganic acids arise as the tissues are disintegrated; these acids combine with the ammonia, and lead to the excretion of much of it in the urine. On the other hand, the liver seems in starvation to lose its power of forming urea out of ammonia.

(*g*) *The Temperature of the Blood.*

Cetti's (1) temperature hovered between 36·4° C. and 37·0° C.; Breithaupt's between 36·3° C. and 37·6° C.; Succi's (13) between 36·2° C. and 37·3° C.; only in the case of Johansson's (4) patient were higher figures sometimes observed in the morning hours (up to 38·2° C.). According to Jürgensen's (14) old and most carefully compiled records of temperature in starvation, and according to the numerous observations taken from starving animals, this small increase in the temperature of the body would appear to be a rare exception. Johansson's patient was known to have an unusually high temperature; on normal days it averaged 37·2° C. and 37·46° C.

7. Influence of Starvation and Underfeeding on the Urine.

1. *The Quantity of Urine.*—During starvation the average amount of the urine remains subnormal, even when the consumption of water is unlimited. As a rule, starving people drink little water; Cetti drank by choice about 1,200 c.c., and his urine averaged 900 c.c. Breithaupt drank 1,540 c.c., and his urine averaged 1,260 c.c. (1). Succi took 1,500 to 700 c.c. daily, and passed on an average 445 c.c. of urine (13). In the experiment on Succi at Vienna the amount of urine sank, with considerable variations, from 1,435 c.c. on the first day of fasting down to 235 c.c.

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on the twentieth day. In the case of three young girls, who began their fast in a good state of nutrition, I found the quantity of urine in the first three days of starvation, with unlimited supply of water, to be from 600 to 900 c.c. In all these experiments it is very clear that the amount of urine depends upon the amount of water consumed.

The loss of water from the body, including that by imperceptible perspiration, usually exceeds the quantity taken in. This is due to the fact that in starvation, not only does the water which is drunk leave the body, but also that which is set free through the disintegration of the tissues; and so, too, does the new water formed by the oxidation of protein. Thus, the percentage of dried substance in the body remains nearly stationary [Voit (139), E. Hofmann (140)]. But this statement only holds good for long periods of time; when an unlimited supply of water is taken, it may on certain days exceed the excretion of urine, so that no weight is lost, or even, paradoxical though it seem, a temporary increase of weight may be recorded [Tuczek (41)].

When, however, the thirst in starvation is not satisfied, the loss of water through the urine, the skin, and the lungs, is greater than the supply arising from the tissues. In consequence, the body suffers from a corresponding impoverishment in water. This may frequently be observed at the bedside—for instance, when a patient refuses food and drink on account of caustic injury to the upper parts of the alimentary tract. The excretion of urine then falls to 500 c.c. or less; the skin becomes dry, the blood concentrated, and cramps in the legs may occur as they do in cholera. Should the difficulty in swallowing disappear in a few days, the patients drink water without restraint; the excretion of urine increases not at once, but after a few days—a sign that the body lacked water and eagerly absorbed it in large quantities. Just the same is to be observed in experiments where the supply of solid nourishment is maintained, and only the supply of water is considerably reduced [Dennig (141)].

In cases of chronic underfeeding the conditions vary greatly. Many persons, when in a state of malnutrition, have a distaste for drinking; they excrete but little urine, and that seldom, and it deposits urates on cooling. Others — and according to my observations they form the majority—do exactly the reverse, so that no fixed rules can be laid down.

2. *Total Nitrogen.*—See Metabolism of Protein.

3. *Urea and Ammonia.*—In starvation, as under ordinary circumstances, the greater part of the nitrogen leaves the body in the form of urea. There are, however, certain slight differences, for conditions are present in starved tissues which augment the excretion of ammonia at the expense of the urea. Hence less than the normal 85 to 88 per cent. of the nitrogen appears in the urine as urea, and more than the normal 2 to 5 per cent. as NH_3. For example, Voges (142) investigated the case of a female patient with melancholia who took nothing but fluids containing a small percentage of solid matter. On the second, fifth, and eighth days of her fast she excreted 16·3 per cent., 13·5 per cent., and 13·6 per cent. of her urinary nitrogen in the form of NH_3, the total nitrogen being 4·86, 5·94, and 5·38 grammes, the nitrogen as NH_3 0·792, 0·802, and 0·732 gramme.

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In a muscular man with gastric ulcer (without hæmorrhage), during four days of starvation, while water only was being given :

	Day of Fast.			
	1.	2.	3.	4.
	Gm.	Gm.	Gm.	Gm.
Total nitrogen ..	10·2	11·8	9·9	8·6
Nitrogen as urea ..	8·57	9·5	7·5	6·3
Nitrogen (Mörner's method)	(84 per cent.)	(81 per cent.)	(76 per cent.)	(74 per cent.)
Nitrogen as NH_3 ..	0·82 (8 per cent.)	0·92 (8 per cent.)	1·4 (14 per cent.)	1·5 (18 per cent.)

In nine young girls (cases of gastric ulceration, some with, some without bleeding, treated by complete abstinence and repeated daily enemata of dilute salt solution) the following were the averages obtained in my clinique by Dr. L. Meyer :

Day of Fast.	*Total Nitrogen.*	*Nitrogen as NH_3.*	*$\frac{\text{Nitrogen as } NH_3 \times 100}{\text{Total N.}}$*
	Gm.	Gm.	
1	8·7	0·61	5·8
2	9·6	1·00	8·5
3	9·6	1·30	11·1
4	10·1	2·10	17·0

Other isolated investigations made on chance occasions upon cases of starving men and women entirely confirm my statements as to this relation between urea and NH_3. All the more remarkable are the constantly small amounts of ammonia observed by E. and O. Freund (26) during Succi's fast at Vienna ; only on one day (the sixth day of fasting) do they rise to 0·934 gramme nitrogen as NH_3, with a total nitrogen of 11·0 grammes. For the rest, they do not surpass the average standard either absolutely or relatively. Also, as the difference between the total nitrogen and the nitrogen as NH_3 was not discovered in the purin bodies, creatinin, or hippuric acid, one must suppose that here a relatively larger part of nitrogen was excreted in the form of amido-acids. The figures for nitrogen and nitrogen as urea were, according to Freund :

Days of Fast.	*Total Nitrogen.*	*Nitrogen as Urea (Mörner's Method).*
	Gm.	Gm.
1–5	60·74	53·82=88 per cent.
6–10	45·71	30·34=88 ,,
11–15	28·01	23·27=83 ,,
16–20	22·23	15·26=69 ,,

According to my experience, there is almost invariably a relative decrease of urea, and an absolute as well as a relative increase

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in the ammonia. The reason for this lies in the fact that in starvation, owing to the breaking-down of the tissues, many acids (phosphoric, sulphuric, aceto-acetic, and β-oxybutyric acids) are set free, the fixed alkali not being sufficient to combine with them. The acids then appropriate to themselves a part of the ammonia formed by the decomposition of protein, and prevent its conversion into urea. The amounts of acetone bodies generated in starvation do not stand in any fixed relation to the completeness or the duration of the fasting, but are also materially affected by factors peculiar to the individual [L. Mohr, G. Satta (143)]. Thus, it is easily understood that the quantity of ammonia excreted varies in different cases of starvation.

For chronic underfeeding there exist hardly any trustworthy statistics. In a number of poorly-nourished gastric cases (chronic catarrh of the stomach and gastric ulcer) I sometimes found 8 to 10 per cent., and once as much as 12 per cent., of the nitrogen in the urine in the form of ammonia. In each case there was an increase of acetone, and in the ethereal extract of the urine small quantities of aceto-acetic acid were discovered. But, as a rule, the amount of ammonia in the urine of starving persons was normal, and so was the amount of acetone reckoned in centigrammes per twenty-four hours. Here, too, the acidosis, or quantity of aceto-acetic and oxybutyric acids in the blood, determines the extent of the NH_3 excretion. In underfeeding, where the scanty diet contains an excess of carbohydrate, neither acidosis nor an increase of ammonia occurs [F. Hirschfeld (144), L. Mohr (145) referring to acidosis]. An example from my clinique, with analyses by Dr. L. Meyer, will illustrate this. While the patient received a full supply of food the excretion of acetone bodies and of ammonia rose from day to day; when cane-sugar was given, both the acetone and the ammonia markedly decreased.

Day of Fast.	*Addition of Sugar to Diet.*	*Urinary—*			*Reaction with $FeCl_3$.*
		Nitrogen.	NH_3.	Acetone.	
	Gm.	Gm.	Gm.	Gm.	
1	0	4·8	0·39	0·24	+
2	0	5·2	0·50	0·49	++
3	0	4·7	0·88	0·60	++
4	90	7·5	1·22	0·80	++
5	150	6·2	0·63	0·03	0
6	240	6·6	0·34	Trace	0
7	240	5·4	—	Trace	0

4. *Amino-acids* (145A).—In Freund's starvation experiment the urinary amino-acids appear to be increased. Brugsch records similar results (3·7 to 6·9 per cent. in starvation, 2 to 3 per cent. normally). Some investigators find that this holds good also for man. Others contest the point. Hirsch and Plant and Reese find that after subcutaneous injection of, or feeding with, alanin, the alanin reappears in the urine in certain quantities quite independently of the nutritional condition of

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the tissues. The exact origin of the amino-acids of the urine in starvation is as yet undetermined.

5. *Purin Bodies.*—The purin bodies, uric acid and the alloxuric bases, are mainly decomposition products of nuclein; they must not, however, be regarded as an exact measure of the decomposition of nuclein in starvation—firstly, because some of the purin bodies set free by decomposition of the nuclein do not leave the system as uric acid, xanthin, hypoxanthin, etc., but as urea; secondly, because further investigations make it seem probable that certain, though small, quantities of uric acid are formed anew synthetically quite independently of the nuclein [Wiener, denied by Burian and others]. A very close, if not mathematically exact, relation thus exists between the decomposition of nuclein and the excretion of purin bodies, and this lends great importance to the values for uric acid, etc., observed during starvation. Schreiber and Waldvogel (146) believed that they had here found the amount of "endogenous purin-nitrogen" excreted from the body under normal conditions; all the purin-nitrogen appearing in the urine beyond the values observed in starvation they attribute to the purin-nitrogen contained in the food. Burian and Schur (146), however, point out that in starvation the wear and tear of nuclein is abnormally small, because the famishing organism makes but sparing use of its highly-valued nuclein. Hence they believe that the endogenous purin-nitrogen under full diet is more than the excretion of purin bodies in starvation indicates, and in this opinion I concur.

There are very few trustworthy[1] determinations of the uric acid in starvation; those of Freund are the only ones which deal with the purin bodies in their entirety. The figures in the following table stand for uric acid in grammes:

Day of Fast.	*Schreiber and Waldvogel.*		*Hooven and Sollmann* (27).	*E. and O. Freund* (26).		*Monaco* (130).
	I.	II.		Uric Acid.	Total Alloxuric Bodies reckoned as Uric Acid.	
	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
1	0·29	0·72	0·82	0·87	1·26	—
2	0·23	0·40	0·62	—	—	—
3	0·20	0·20	0·45	0·60	0·79	—
4	—	—	0·54	0·33	—	—
5	—	—	0·43	0·27	0·47	—
6	—	—	0·43	0·26	—	—
7	—	—	0·37	0·38	0·57	—
8	—	—	0·57	0·33	—	—
9	—	—	0·91	0·26	0·49	—
10	—	—	—	—	—	—
11–15	—	—	—	0·20	0·31	—
16–20	—	—	—	0·22	0·35	0·25

[1] A. Schäfer's (30) accounts of the urine of fasting lunatics, chiefly between the fourth and sixth days of their starvation, deal with the nitrogen of the total alloxuric bodies. On an average, 0·1795 gramme were found in a day. Unfortunately, the analyses were made by the uncertain method of Krüger-Wulff.

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Five separate accounts of the third and fourth days of starvation which are at my command gave 0·23 to 0·36 gramme of uric acid (women). As during the two first days of fasting the amount of the purin bodies is still dependent upon the food previously taken, the figures have no interest before the third day. They differ from each other too much to justify their use as normal values for starvation—either for purin bodies in general or for uric acid in particular—though Schreiber and Waldvogel are of a contrary opinion. In the light of modern views upon endogenous uric acid, the old thesis [Marés, Salkowski, von Noorden (146)], that the amount of uric acid produced was partly determined by individual factors, has become too narrow. Nevertheless, it has not lost its place in a general survey of the values observed in starvation. My former assistants, M. Kaufmann and L. Mohr (146), have furnished proof of this by other investigations in opposition to Burian and Schur.

Impossible as it is to fix any standard quantity for uric acid and the purin bodies excreted in starvation, it is even less possible to calculate from the values ascertained the amount of nuclein consumed during starvation. Under normal conditions of nutrition one is able to determine the excretion of phosphoric acid and to estimate the amount of the decomposition of nuclein by combining the numbers for phosphoric acid and purin [O. Loewi (146)]. But experience teaches us that, besides the nuclein, another tissue rich in phosphorus, that of the bones, is much affected by starvation. It is impossible to decide how much phosphoric acid comes from the nuclein and how much from the bones. And, on the other hand, the fact that uric acid is formed from the hypoxanthin of the muscles, and so excreted [Burian (145A)], makes all these calculations most uncertain.

There is no object in discussing the occurrence of alloxuric bodies in the urine during insufficient food-supply and chronic underfeeding, as it is not the degree and duration of the want of food which decide the matter, but the quantity and type of the diet. Many data, collected at a time when no attention was paid to the presence of the purin-nitrogen of the food, have now lost all value—for instance, the analyses by Cario, von Noorden, C. Brandenburg (146).

6. *Creatinin.*—In normal nutrition the creatin of the food is the most important source of creatinin. Next to that comes the creatin contained in the muscles. For many years nobody doubted but that this creatin, in so far as it was set free by the wear and tear of the muscles, passed into the urine exactly in the same way as the creatin contained in the food. Though for a time violently attacked [G. S. Johnsohn, R. Neumeister (147)], this old theory is gaining ground again. The supposed differences between the creatinin of the urine and that of the muscles, as advanced by G. S. Johnsohn, have not been maintained. A. Gregor (148) showed that the influence of muscular work upon the excretion of creatinin was far more important than had been imagined [C. von Voit, K. B. Hofmann (149)]. E. Poulsson and E. Schmidt have recently proclaimed the identity of the two creatins in the most emphatic and apparently final manner on chemical grounds (148). Also all our experiments in starvation appear to me to support the old teaching that derives creatinin

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from the creatin of the muscles. Undoubtedly creatinin diminishes in fasting, but it does so proportionately to the disintegration of the tissues. This is confirmed by an investigation of Baldi's (150) on the famous Succi.[1]

Day of Fast.	*Nitrogen.*	*Creatinin.*	$\frac{Nitrogen}{Creatinin}$.
	Gm.	Gm.	
7	9·374	0·8011	15
12	7·162	0·7159	10
17	6·160	0·4029	15

The material to hand is very scanty, and does not justify any far-reaching deductions. In any case, it does not contradict the opinion, expressed by Gregor and others, that creatin is a specific product of the muscles and other tissues—the thyroid gland (?) [N. Bubnow (151)]—and is given off in proportion to their wasting [von Noorden (152)]. Whether creatinin is a trustworthy measure for the breaking down of these tissues is a point we cannot determine. As regards periods of chronic inanition, the determinations of creatinin have as yet no definite significance, That it decreases in amount [Hofmann (149)] is explained by the smaller supply of food. Munk states that in convalescence little creatinin is excreted; this gives rise to the question whether it may not be retained to renew the wasted muscular tissues (153). The investigations should be repeated and extended in man, due consideration being given to the amount of creatin present in the diet, for it is not permissible to transfer the results of experiments upon flesh-fed dogs directly to human beings. In the dog fed upon meat the excretion of creatin decreases—even on the first and second days of starvation—to nearly the tithe of its former value; to this there is nothing analogous in human beings [M. Gruber (154)].

7. *Salts.*—During starvation salts are excreted in the measure in which they enter the circulation after being set free by the disintegration of the tissues and by the decomposition of protein. Here they are not able to remain, because the organs of excretion, especially the kidneys, watch carefully over the amount of salts in the blood, and at once remove any superfluity. This has long been known, and was confirmed by von Koranyi (155), who found normal relations between the lowering of the freezing-point of the blood and of the urine during the first twenty days of Succi's fast. From that point onwards the osmotic pressure of the urine decreased in contradistinction to that of the blood. At the same time albuminuria appeared; the diseased kidneys were no longer able to perform their functions with regularity. The absolute extent to which the freezing-point is lowered naturally falls in the urine of starvation, because

[1] In Succi's fast at Vienna the excretion of creatin was much more irregular. Unfortunately, E. and O. Freund used Kolisch's method, which is not free from objection.

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the amount of NaCl in it decreases rapidly. Conversely, as the other urinary salts do not decline in the same proportion as the NaCl, the quotient $\frac{\Delta}{\overline{NaCl}}$ rises [Koranyi (155), Waldvogel (156)].

Koranyi found the quotient $\frac{\Delta}{\overline{NaCl}}$ to be as follows :

The normal value	1·23–1·69
On first day of fast	1·56
On tenth day of fast	16·20
On sixteenth day of fast	21·49
On twenty-ninth day of fast	70·00

In exact accordance with the large or small quantity of the salts contained in the material sacrificed in starvation, so will each separate salt leave the body in larger or smaller amount by the paths of excretion. And the ratios in which the excreted salts are mixed, combined with the knowledge of the amount of ash left by the different tissues, afford proofs as to which tissues, organs, and portions of organs are being subjected to decomposition. These are the considerations which make the study of the changes in the salts during starvation interesting and important.

(*a*) *Chlorides.*

Common salt, and its chlorine in particular, diminish more than the other mineral constituents in starvation. The excretion of chlorine by other means (sweat and fæces) is so slight during starvation as to be a negligible quantity. Whether considerable amounts of chlorine are excreted during the first day or two of starvation, or whether the values immediately approach the minimum characteristic of starvation, depends upon the extent to which the body is saturated with chlorine and upon its previous nutrition. The dog, as a carnivore, consumes little salt, and even on the first day of starvation parts with only an extremely small amount of chlorine [C. von Voit, F. A. Falck, J. Munk (157)]. With man, who generally consumes a large amount of common salt, and therefore harbours in his blood and the fluids of his organs a superabundance of chlorine, several days often elapse before this superfluity is got rid of (see table, p. 41).

Besides these systematic investigations, many scattered records exist [for instance, Fr. Müller (20), Tuczek (41), Hooven and Sollmann (27), Koranyi (155), Nebelthau (21), and others]. The lowest values were found by Daiber (86) during the last days of a twenty days' fast —0·2 to 0·27 gramme; on the last day the traces were too small for estimation.

The low percentage of chlorine present in the urine of starvation is due to the fact that the disintegrating tissues, especially the muscles, contain only small amounts of sodium chloride. It is not certain whether any more common salt is excreted in addition to that naturally contained in the wasting tissues, so that the starving body experiences a loss of

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NaCl, which is not only absolute, but also relative. Munk (157) believes this to be the case, as—in contradiction to the earlier observations of Voit and Falck (157) on the dog—he confirmed Tuczek's statement that marked retention of NaCl occurs in man when nutrition is resumed.

The quantitative relations of the sodium chloride to the tissue-protein (0·4 gramme chlorine in 1,000 grammes muscular tissue) make the ratio of the chlorine to the nitrogen in the urine of importance in determining the degree of inanition. As long as several grammes of NaCl are present in the urine the body is not living entirely at the expense of its own tissues, which are poor in NaCl. If several grammes of NaCl are found in the urine of a man who says he is starving, there is reason to suspect him of malingering; ordinary food is rich in common salt, and this rapidly reappears in his urine.

	Breithaupt.	*Cetti.*	*Succi, I.* (*Luciani*).	*Succi, II.* (*Freund*).
Before the fast ..	5·55	5·4	6·3	—
1st day of fast ..	3·92	1·61	1·35	5·45
2nd „ „ ..	1·1	2·3	0·54	1·83
3rd „ „ ..	0·85	1·7	(1·16)*	0·93
4th „ „ ..	0·75	1·5	0·85	0·89
5th „ „ ..	0·44	1·4	0·82	0·71
6th „ „ ..	0·35	1·1	(0·84)*	0·78
7th „ „ ..	—	0·95	(0·80)*	0·67
8th „ „ ..	—	0·84	0·74	0·67
9th „ „ ..	—	1·1	0·54	0·71
10th „ „ ..	—	0·6	0·51	0·53
11th „ „ ..	—	—	—	0·36
12th „ „ ..				

NOTE.—Succi drank, on certain days marked *, 150-200 c.c. of Riolo mineral water, which contains about 2 per cent. NaCl.

In chronic underfeeding the amount of NaCl naturally sinks below the normal 12 to 15 grammes, or, with milk diet, 7 to 8 grammes. But no general rules can be laid down as to what extent this takes place; in some cases it depends upon the decrease in the food, and also upon any individual preference for taking either more or less salt with the food. In a large number of ill-nourished people with small appetites, but without special diseases which would influence metabolism, I have investigated the NaCl and N of the urine, and found them on the whole to coincide with the normal relations given in the text-books—viz., 1 part of NaCl to 2 of urea. Hence it is to be concluded that in malnutrition the input and excretion of NaCl diminish in proportion to the limitation of the food, and, more particularly, to the supply and decomposition of protein.

It is quite otherwise when chronic starvation is pushed to the limits of complete inanition. Under these conditions a relatively small amount of protein in the food, rich in NaCl, and a large amount of tissue-protein which is poor in NaCl, are decomposed, with the immediate result that the urine contains little chlorine. Thanks to their miserable diet, such persons have long since parted with any excess of NaCl, such as is to

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be found, according to C. von Voit, in the tissue fluids of the healthy, well-fed body. Should such an excess be present during a period of total abstinence, which may occur, for example, in the closure of a previously incompletely stenosed œsophagus, then the quantity of NaCl in the urine immediately dwindles to less than that of the healthy starving man, and is often to be reckoned only by centigrammes each day [Gärtig, von Noorden (158)]. The long-continued want of food has made the body poor in chlorine and hungry for it ; any common salt given is greedily retained. In a patient with narrowing of the gullet due to poisoning with sulphuric acid, who came into the hospital almost a skeleton, no measurable amount of chlorine was found in the scanty urine. On each of the three following days subcutaneous injections of 1,500 c.c. were given, each containing 0·9 per cent. of NaCl and 10·0 per cent. of grape-sugar (= 40·5 grammes NaCl in three days). During this time 1,950 c.c. of urine were excreted, the whole of which contained 6·5 grammes of NaCl only. Gluzinski records a similar observation. These facts all agree with Munk's investigations of Cetti and Breithaupt, which led him to the deduction that even in cases of acute starvation the body is quickly impoverished in chlorine.

(*b*) *Potassium and Sodium.*

The normal ratio between sodium and potassium in the urine of a healthy man under normal diet is on an average 64 : 36. This is the mean of the figures given by Salkowski, Stadelmann, Beckmann, and Bunge (160). It corresponds with the proportion in which the two substances occur in the food. In health any alteration here can only arise from abnormal conditions of diet. Thus, with a diet consisting entirely of meat rich in potassium, Bunge (161) found almost as much potassium as sodium in the urine (3·308 grammes K to 3·991 grammes Na).

In starvation this relation is reversed, for the tissues which first begin to waste, the muscles and the glands, are rich in potassium and poor in sodium. The ash left when the body is incinerated contains 3 parts of potassium to 1 of sodium. It is natural that a preponderance of potassium should not be looked for with confidence until several days have elapsed, when the slight excess of NaCl originally present will have been got rid of (see table, p. 43).

The figures demonstrate that in starvation, with the lapse of time, the ratio of potassium to sodium approaches that in which they are found in the ashes of the tissues. When the fast is over it returns to its normal value on the first, or at latest the second, day after food has been taken [Munk (157)].

This reversal of the normal ratio of potassium to sodium is characteristic when the body is living entirely or preferably on its own tissues. It will not be the case where the underfeeding, though considerable, can be endured, for even with a scanty diet a man takes in and excretes much NaCl. Thus a lunatic who ate only in very small quantities excreted more sodium than potassium—0·625 and 0·80 gramme potassium and 0·862 and 1·755 grammes sodium. I obtained similar figures with a

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female patient who, on account of non-febrile appendicitis, took only 1 litre of liquids daily (partly milk, partly broth, and partly vegetable soup with an egg); the average excretion on three successive days, the eighth to tenth of her illness, was 1·92 grammes potassium and 2·85 grammes sodium. These isolated observations of course do not preclude the possibility that in other cases of underfeeding the ratio may be exactly reversed. That would occur if a large quantity of tissue-protein was broken down through lack of nutriment. As a matter of fact, this does happen in febrile diseases where a toxic decomposition of protein takes place.

Day of Fast.	*Cetti.*		*Breithaupt.*		*Succi (Freund).*	
	K_2O.	Na_2O.	K_2O.	Na_2O.	K_2O.	Na_2O.
	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
1	—	—	1·8	2·2	—	—
2	—	—	1·6	0·8	—	—
3	—	—	1·4	0·6	—	—
4	2·8	1·3	1·1	0·5	2·5	3·3
5	—	—	0·8	0·2	—	—
6	—	—	0·9	0·2	—	—
7	2·0	0·7	—	—	—	—
8	—	—	—	—	3·7	1·9
10	0·5	0·5	—	—	—	—
13	—	—	—	—	1·3	1·0
18	—	—	—	—	1·3	0·6
The normal values	2·6	3·7	1·5	4·7	—	—

(c) *Phosphoric Acid.*

Were the muscles and glands the only nitrogenous tissues that decomposed, the proportion of nitrogen to P_2O_5 in the excreta would be about as 6·6 to 1. Instead of this, both in animals [J. Munk (163)] and in men the proportion is much smaller:

Tuczek (41), in starving lunatic women, found 6·0 and 4·3 to 1.

Fr. Müller (20), under the same conditions, 3·8 to 1.

Luciani (13), in Succi's first ten days of fasting, 5·68 to 1; in the second ten days, 5·58 to 1.

Freund (26), in Succi's first ten days, 4·46 to 1, average 10·74 grammes nitrogen and 2·41 grammes P_2O_5; in the next ten days, 4·57 to 1, average 5·024 grammes nitrogen and 1·10 grammes P_2O_5.

Hooven and Sollman (27), in eight days of starvation, 5·4 to 1, average 14·12 grammes nitrogen and 2·60 grammes P_2O_5.

The ratio between the nitrogen and P_2O_5 excreted becomes still smaller when one considers the amount of the fæces in starvation. This is indispensable, because in proportion to their nitrogen the fæces contain much P_2O_5 (with Cetti, 3·164 grammes nitrogen and 2·05 grammes P_2O_5 in ten days; with Breithaupt, 0·68 gramme nitrogen and 0·841 gramme

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P_2O_5 in six days of starvation). Including the fæces, the ratio in Cetti's ten days was 4·4 to 1, the totals averaging 11·57 grammes nitrogen and 2·62 grammes P_2O_5 a day. With Breithaupt the ratio gradually sank from 6·4 to 1 on the first day of starvation to 4·3 to 1 on the sixth day.

C. von Voit had already supposed that the relatively larger excretion of P_2O_5 came from the bones, which lost in size thereby [Sedlmair, M. Gusmitta (165)]. But J. Munk (163) was the first to prove this by his classical experiments on man and beast. He demonstrated that the relative increase of the phosphoric acid in starvation was accompanied by a contribution of earthy matter from the bones in the form of lime and magnesia. This puts an end to Edlefsen's (35) assumption, which has long seemed unlikely, that the richness of the urine of starvation in P_2O_5 arose from the phosphorus-rich nervous tissues.

In complete starvation the facts as to the elimination of P_2O_5 are clear enough, but with merely insufficient nutrition matters become very complicated. There exist numerous records as to the nitrogen and P_2O_5 in the urine, and few concerning the fæces. But there is nothing which bears upon the only important questions—namely, does the body when in a state of under-nutrition excrete more P_2O_5 than is accounted for by the supply and the contingent decomposition of the tissue protein, and does it, therefore, suffer loss from the breaking down of tissues rich in phosphorus, namely, the bones? To answer these questions accurately, balance-sheets of the nitrogen, P_2O_5, CaO, and MgO in the food and in the excretions are necessary. As yet we have no such balance-sheets. The observation that in underfeeding high values are often found for the lime in urine and fæces certainly leads one to suppose that the P_2O_5 balance-sheet will reveal corresponding losses. The minimum demand for phosphorus seems to lie between 1 and 2 grammes daily [R. Ehrström (165A)].

(*d*) *Lime and Magnesia.*

As a rule, more magnesia than lime is excreted by a normally-fed man. Animal foods and certain vegetables are poor in lime and rich in magnesia. Hence it is that the kidneys excrete only a small part of the lime, the greater part of it leaving the body in the fæces [Bertram, von Noorden and Belgardt, G. Herxheimer, G. Renvall (166)]. In starvation a considerable increase takes place in the quantity of the lime compared to that of the magnesia, and it may not only reach, but even surpass in absolute amount, the quantities found in the urine and fæces on full diet (see table on p. 45, in which these quantities are given in grammes).

The proportion of lime to magnesia in the excretions, urine and fæces, is, as J. Munk (1) showed, nearly the same as that found in the bones. Taken in conjunction with what had been ascertained about the excretion of phosphoric acid, this justified Munk in assuming that the bones disintegrate during starvation.

Less lime may appear in the fæces than in the urine of starvation. Thus Cetti in ten days excreted 0·97 gramme CaO in the fæces,

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3·91 grammes (= 80 per cent.) in the urine; Breithaupt in six days passed 0·265 gramme CaO in the fæces, 0·91 gramme (= 77 per cent.) in the urine. This fact may be due to a variety of causes. In the first place, the fæces of starvation are devoid of the lime that would normally have reached them in the food, and of which a certain percentage would have escaped reabsorption. And, in the second place, the presence of abnormal acids in the blood during starvation must also be borne in mind; they facilitate the excretion of lime by way of the kidneys [D. Gerhardt and Schlesinger (167)].

Day of Fast.	*Cetti* (1).		*Breithaupt* (1).		*Succi* (26).	
	CaO.	MgO.	CaO.	MgO.	CaO.	MgO.
	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
1	—	—	0·073	0·217	0·25	0·33
2	—	—	0·202	0·116	—	—
3	0·446	—	0·194	0·148	—	—
4	0·470	0·297	0·161	0·123	0·196	0·25
5	—	—	0·134	0·120	—	—
6	—	—	0·145	0·144	0·39	0·53
7	—	—	—	—	—	—
8	—	—	—	—	0·49	0·16
9	0·322	0·162	—	—	0·27	0·20
10	0·277	0·179	—	—	—	—
11	—	—	—	—	0·31	—
13	—	—	—	—	0·27	0·24
18	—	—	—	—	0·11	0·08
Before the fast ..	0·342	0·384	0·202	0·217	—	—

How far these relations of the alkaline earths, the diminution in the earthy constituents of the bones, and the increase of the lime in the urine, are applicable to incomplete inanition and chronic underfeeding cannot at present be determined. It is true that there exist a large number of estimations of the lime, and a smaller number of estimations of the magnesia, in pathological urines [Neubauer-Vogel, G. Hoppe-Seyler, Senator (168), and others]. They mainly concern individuals in a bad state of nutrition. The figures vary widely, but the majority of the analyses show abnormally high values for the lime. Most important is Beneke's (169) discovery that in all conditions of debility enormous quantities of earthy phosphates (2 to 4 grammes) appear in the urine quite independently of the nature of the disease or of the nourishment. Trustworthy deductions can only be made by carefully worked out balance-sheets. The lime-salts of the urine are far too small and variable in quality for the estimation of the total amount excreted, and the total output tells us nothing unless the intake also is known. The very exact observations of Ott (177) are important for certain aspects of pulmonary tuberculosis, but they cannot be turned to account for our present purpose because his patient was being well fed. The works published by other authors leave it uncertain how much was due to

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disease and how much to starvation—in the case of diabetes mellitus, for example. In the case of the female patient with a febrile appendicitis already mentioned, I found that during three days the intake of lime was 6·2 grammes, the output 7·7 grammes, the fæces containing 6·7 grammes. The relation between the fæcal and urinary lime-salts thus remained normal; no acidosis was present, the urine giving no reaction with perchloride of iron. It is unfortunate that the magnesia determination went amiss. These isolated determinations hardly yet justify the conclusion that moderate degrees of malnutrition favour the absorption of osseous tissue as acute starvation does. Perhaps Hoppe-Seyler's (168) interpretation is preferable—viz., that rest in bed *per se* favours the excretion of lime-salts, while the bones slowly atrophy from disuse.

(e) *Sulphur.*

The source of the sulphur appearing in the urine is identical with that of the nitrogen. Both are derived from the protein; hence during starvation their excretions should run parallel and in the same ratio as that in which they are present in protein. Exact parallelism is hardly to be expected, because the various forms of protein all contain much the same percentage of nitrogen, but varying amounts of sulphur. Hence the ratio N : S will depend upon the protein that is undergoing cleavage. On the average, protein contains 1 part of sulphur to 14 to 16 parts of nitrogen.

The only experiments in which the total sulphur excretion was measured are those on Cetti and Breithaupt. Here the ratio S : N was = 1 : 14·7 to 15·1. In all other fasting experiments, particularly Succi's fasts at Florence and Vienna, the sulphates were estimated, but the neutral sulphur was neglected. Luciani gives the ratio 1 : 17·1; Freund, for the first ten days, gives 1 : 19·5 (= 0·55 gramme sulphur to 10·74 grammes nitrogen), for the second ten days, 1 : 20·1 (= 0·25 gramme sulphur to 5·024 grammes nitrogen). Considering that a relative increase takes place in the neutral sulphur excreted during fasting [J. Munk, Savalieff, H. Benedict (169)], and making the additions thus indicated to the value for sulphur calculated on the measured amount of the sulphates excreted, then figures result that correspond with those of the experiments on Cetti and Breithaupt.

The special relations of the sulphuric acid esters in starvation are stated elsewhere. Only the most important figures are given here:

	Period of Fast (Days).	*Average Total Sulphur.*	*H_2SO_4 Esters.*	*Ratio.*
		Gm.	Gm.	
Cetti	10	1·75	0·17	10·3 : 1
Breithaupt ..	6	2·21	0·244	9·0 : 1
Succi (Freund) ..	1–10	1·65	0·133	12·4 : 1
„ „ ..	11–21	0·76	0·089	8·5 : 1

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(*f*) *Reaction of the Urine.*

The reaction quickly becomes more acid in all fasting experiments [Fr. Müller, Luciani, Freund]. After various intervals—six to ten days—the acidity falls to, or even below, the normal value. I found a continued increase in the acidity in most, though not in all, of the cases where the starvation lasted over four days.

The reason for this is not clear. It is admitted that acids continue to be produced in the fasting body; sulphuric, uric, aceto-acetic, and oxybutyric acids may be mentioned. Phosphoric acid, too, reaches the circulation, being set free without any corresponding alkali by the decomposition of nuclein. It will be remembered that carnivores and human beings have a supply of NH_3 always at hand to combine with these acids.

The alkalinity of the urine was determined by the method of Freund and Töpfer only in Succi's Vienna experiment. For the first ten days it remained at the normal level of 1·0 gramme NaOH, and then sank; by the twentieth day it had only half that value, or even less, the calculation being made for the total excretion of the twenty-four hours.

(*g*) *Acetone Bodies.*

Eleven years ago I described the acetonuria of inanition in my textbook of the "Pathology of the Metabolism" (p. 176). Since that date our views as to the origin and significance of the acetone bodies have changed materially, but the facts then recorded have received uniform confirmation.

At the present time it is admitted that neither the carbohydrates nor the protein—whether of the foods or of the tissues—are the chief sources of acetone in the organism. It is true that in the test-tube strong oxidizing agents yield traces of acetone from the albuminates [F. Blumenthal and C. Neuberg, Orgler, R. Cohn (171)], and that the transformation of the carbohydrates into acetone is theoretically possible. It must be conceded that small quantities of acetone may have such an origin, but the acetone bodies met with in inanition or in diabetes mellitus are almost exclusively developed in close connection with the breaking down of fat.

Their chief sources are the lower (and to a smaller extent also the higher) acids of the fatty series. It is probable that the acetone bodies are intermediate members formed during the breaking down of fat [H. Chr. Geelmuyden, A. Magnus-Levy, L. Mohr (173)], oxybutyric acid being first formed, and passing through aceto-acetic acid into acetone, CO_2, and HO_2. In this way small quantities of the very volatile acetone would be caught up by the lungs and expired, smaller amounts being excreted by the kidneys.

Lack of carbohydrate in the diet leads to acetonuria, while the consumption and decomposition of carbohydrate diminish or prevent it. This fact was demonstrated long ago by G. Honigmann, G. Rosenfeld, and others (174), but its importance was not fully recognised before

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F. Hirschfeld's paper (175) appeared. Different views have been expressed as to its interpretation.

Waldvogel (176), on the one hand, believes that only the fat-sparing influence of the carbohydrate is concerned. If carbohydrate is present in the circulation, the amount of fat decomposed lessens; whether it be fat from the tissues or fat from the food is indifferent. With the diminishing decomposition of fat there is a corresponding diminution in the production of acetone bodies, according to Waldvogel. Yet there are important objections to his view. Experience shows that a relatively small addition of carbohydrate—about 100 grammes a day—to a meat diet, or in starvation, at once puts an end to the acetonuria, or at any rate diminishes the amount of acetone from 1 to 2 grammes to a few decigrammes or even centigrammes per diem. But 100 grammes of carbohydrate can only lessen the consumption of fat by 44 grammes at most theoretically, and practically by no more than 30 to 35 grammes. A small amount of muscular work would at once send up the decomposition of fat to its former level, or even above it, in spite of the carbohydrate added to the diet, and so, according to this theory, increase the acetonuria. As a matter of fact, however, this increase does not take place.

On the other hand, a second theory appears even in Hirschfeld's earliest work (175), and has been subscribed to by other writers. According to this view carbohydrates have the power of facilitating the normal breaking up of the fat-molecule. By the simultaneous combustion of carbohydrate, perhaps even by its mere presence [von Noorden, L. Mohr (173)], the decomposition of the fat is enabled to continue till the end-products C_2O and H_2O are formed (with the exception of small amounts of acetone arrested by the lungs and kidneys). But if carbohydrates are absent, certain parts of the fat form the acetone bodies which are excreted from the body through various channels. It remains an open question whether the acetone bodies are formed in normal amount, but fail to be entirely oxidized because no carbohydrate is present, or whether only the lack of carbohydrate determines that the fat should break down in such a way as to form them. In the one case the metabolism would merely be impaired quantitatively; in the other, its intermediate steps would be altered qualitatively. Mohr (173) argues that in diabetes the latter process probably has a hand. It is not known in what way carbohydrates assist the normal breaking down of fat; that they do assist it was long ago shown by O. Nasse (177) to be probable. Quantitative relations must, of course, exist between the supply of carbohydrate available and the variations in the decomposition of the fat; their existence is indicated by the fact that the acetone bodies increase whether the carbohydrate be diminished or the fat in the diet be much augmented. The rule holds that carbohydrates undergo combustion in the organism in preference to other kinds of food, but they can be economized at the expense of fat if the mass action of great quantities of fat in the food be set to work. Under such circumstances the acetone must increase in the urine just as it would if the supply of carbohydrate in the diet were diminished. Quite apart from the food, events will also be regulated by the amount and distribution of the carbohydrate—glycogen—stored in

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the body ; these, however, are factors that cannot be evaluated. Hence it is not surprising that when the juices of the tissues are flooded with fat the acetonuria should increase greatly in some cases and remain almost unaltered in others ; the very different opinions expressed on this point by Geelmuyden, G. Rosenfeld, Waldvogel, and Hagenberg, L. Schwartz, Schuman-Leclerq, and L. Mohr (178) may be compared.

The cause of acetonuria, then, is recognised to be a diminution of the supply of carbohydrate on the one hand, and a relative decrease of the amount of carbohydrate decomposed as compared with that of the fat broken down on the other. Hence acetone bodies are excreted to a considerable extent during starvation. Isolated observations on the presence of acetone and diacetic acid in the urine during inanition were published years ago by von Jaksch, Siemens, Külz, Tuczek, and Fr. Müller (179) ; exact knowledge about the matter was first obtained by experiments upon the professional fasting men.

The following table gives the urinary acetone in grammes :

	Cetti.	*Breithaupt.*
	Gm.	Gm.
Before the fast ..	0·015	unweighable
1st day of fast ..	0·530	0·064
2nd „ „ ..	0·706	0·109
3rd „ „ ..	0·773	0·215
4th „ „ ..	0·784	0·407
5th „ „ ..	0·657	0·575
6th „ „ ..	—	0·506
7th „ „ ..	—	—
8th „ „ ..	0·627	—
9th „ „ ..	0·565	—
10th „ „ ..	0·671	—
Food taken : 1st day ..	0·357	0·114
„ 2nd „ ..	0·201	0·005

The later researches of F. Hirschfeld, J. Müller, Nebelthau, Waldvogel (180), and others, confirm these facts, and show that large individual variations occur in the excretion of acetone. Waldvogel (181), for example, found only 0·005, 0·0066, and 0·062 gramme of acetone and aceto-acetic acid together in the urine of a well-nourished student during the first three days of his fasting ; β-oxybutyric acid was absent. My assistant, L. Mayer, on the other hand, found 0·711, 1·483, and 1·990 grammes of acetone in the urine of a well-nourished girl who came into the hospital on account of gastric ulcer and slight hæmorrhage, during her first three days of starvation, while 48·8 grammes of β-oxybutyric acid were excreted during that period. Such differences as these can hardly be explained by variations in the amount of glycogen contained in the body ; individual peculiarities in the energy with which oxidation proceeds must exist.

With the inclusion of the acetone leaving the body by the lungs its total amount is increased, probably by 20 to 40 per cent. During normal nutrition the greater part of the acetone is excreted in the breath, and this is also the case when fat is added to the diet and the formation of

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acetone grows larger. But during starvation this relation is commonly inverted [J. Müller, Schuman-Leclerq, Schwarz, Waldvogel],[1] for the urinary acetone is considerably more than that expelled by the lungs.

As regards the other acetone bodies, one usually finds a marked aceto-acetic reaction with perchloride of iron during the first day of starvation. I have generally found the reaction very strongly marked after thirty-six hours. The reaction can be obtained as long as the fast continues. Its first appearance is rarely deferred to the second day, and if it is, the conclusion that the body had a large reserve of carbohydrate at its disposal is justified.

Külz (179) was the first to find β-oxybutyric acid in the urine of starvation. At the present time nobody can question the fact that when food is withheld for long periods very considerable quantities of this acid may appear in the urine. The highest figure is that given by D. Gerhardt and W. Schlesinger, who found 40 grammes a day in the urine of a woman with hysterical vomiting. Nebelthau (21) describes an analogous case in which only 0·14 to 0·18 gramme of the acid were excreted. In muscular men who fasted, Waldvogel found that during the first three days of the fast the daily excretion of the sodium salt of the acid varied from a few decigrammes up to 3 grammes. My assistant, L. Meyer, found from 2·4 to 16·3 grammes a day during the first three days in the urine of young women who received no food at all on account of gastric ulceration. So here too, as in the case of acetone, the individual variations are large.

Carbohydrate feeding diminishes or even abolishes acetonuria very rapidly. This fact is of great importance to the whole theory of the acetone bodies, and is of equally great practical value. From 100 to 120 grammes of sugar suffice for the purpose; all the other phenomena due to starvation continue unaltered. The decomposition of protein is unchanged, the metabolism of the fat is lessened almost imperceptibly, but the excretion of acetone bodies sharply diminishes. F. Hirschfeld (175) was the first to remark that acetonuria depends upon lack of carbohydrate, not upon malnutrition or the breaking down of the tissues; his statement has received full confirmation [E. Rosenfeld, Waldvogel, Jorns (183), L. Mohr, and others]. Only a single acetonuria is known, and that is due to want of carbohydrate; it is no longer justifiable to speak of an acetonuria due to starvation, or to contrast it with other forms of the excretion of acetone bodies.

A few illustrative cases may be given from my own clinique. They concern patients who were given no food at all on account of gastric ulcer

[1] On the strength of this phenomenon, Waldvogel (181) endeavoured to show how carbohydrate lessens the production of acetone. His hypothesis can satisfy nobody, and it seems to me that the real interpretation is much simpler. When the diet is normal, or when fat is added to such a diet, decomposition of the fat is never arrested at the point where aceto-acetic acid is formed, but always proceeds further to the production of acetone. Acetone is volatile, and is readily caught up and expired by the lungs in relatively large proportions. But during starvation, and particularly if carbohydrate is withheld, aceto-acetic acid circulates in the blood as well as acetone, and this acid can be excreted by the kidneys only, not by the lungs. It is estimated in the urine by distillation, coming over with the acetone. So the greater the amount of aceto-acetic acid is, the greater will the quantity of acetone in the urine be as compared with that in the expired air.

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or some similar condition, and who received *eau sucrée* on and after the fourth day. It so happened in the third case quoted below that an attack of articular rheumatism with high fever occurred while the observations were in progress; this is a lesion which was bound to increase the urinary acetone by producing a "febrile acetonuria," according to earlier views. But this, notwithstanding, is just the case that best illustrates the favourable influence of the carbohydrate administered.

Case.	*Day of Fast.*	*Nitrogen.*	*Acetone.*	*β-Oxybutyric Acid.*	NH_3.	*Glucose added to Diet.*
		Gm.	Gm.	Gm.	Gm.	Gm.
I.	1	9·2	0·71	48·8	0·57	—
	2	11·5	1·44	48·8	1·84	—
	3	8·0	1·99	48·8	1·43	—
	4	(?)	(?)	8·8	(?)	100
	5	5·4	0·87	8·8	1·67	100
	6	3·16	0·24	8·8	0·75	100
	7	2·69	0·09	—	0·38	100
II.	1	10·36	0·23	2·40	0·82	—
	2	9·53	0·30	2·40	0·65	—
	3	9·38	0·47	2·62	1·45	—
	4	9·82	0·01	1·13	1·23	120
	5	7·48	0·07	1·13	0·36	120
III.	1	8·96	0·04	—	0·81	—
	2	7·30	0·54	—	0·63	—
	3	8·51	1·13	—	1·34	—
	4	8·82	1·66	—	1·46	—
Fever	5	5·87	0·63	—	1·18	120
	6	8·69	0·11	—	0·67	240
	7	8·14	trace	—	0·42	240

A condition of partial inanition may result from a diet containing protein and fat in quantities sufficient to meet the demand of the body for heat, but lacking in carbohydrate. Such a diet may lead to the excretion of acetone bodies identical in nature and quantity with those found during complete abstinence from food [G. Rosenfeld, F. Hirschfeld, Gerhardt and Schlesinger, L. Mohr, and others]. This may be exemplified by observations made in my clinique by G. Satta (183A) upon a healthy man (see table, p. 52).

During the first four days the heat value of his food was adequate. None the less, the lack of carbohydrate made the excretion of acetone bodies rise to a height at least equal to that observed in starvation, and even surpassing its average value. Addition of rice to the diet was followed by a sudden decrease.

Although systematic observations extending over long periods of fasting are still to seek, it appears that the amount of the acetone bodies excreted grows larger as the starvation continues.[1] On a diet of protein

[1] Brugsch has just published the following figures for the twenty-third to the thirtieth day of starvation:

Average, 9·27 grammes oxybutyric acid.
" 0·40 gramme acetone.

A female suffering from stenosis of the œsophagus, wasted to a skeleton (at the autopsy not a trace of fat was demonstrable). For nine days prior to the operation she

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and fat the opposite is the rule. The excretion augments very rapidly at first, remains for a short time at a certain height which varies with different individuals, and then falls slowly to reach normal or nearly normal values. This means that the healthy organism adapts itself to the breaking down of fat as far as to the formation of the normal end-products, either without any carbohydrate, or else with the aid of carbohydrate which has been newly formed in the body [von Noorden, L. Mohr (173)]. Similar observations can be made in diabetes, or at any rate in mild cases of that disease [von Noorden (184)].

Day.	*Food given.*	*Acetone in Urine.*	*β-Oxybutyric Acid.*	*Acetone Bodies calculated as β-Oxybutyric Acid.*
		Gm.	Gm.	Gm.
1	Meat, 200 grammes Fat, 200 „	0·06	0·84	0·95
2	Ditto	0·66	0·73	1·91
3	Meat, 250 „ Fat, 300 „	2·55	3·56	8·73
4	Meat, 250 „ Fat, 250 „	3·11	14·70	20·0
5	Ditto, plus Rice, 150 „	0·06	2·10	2·21

If starvation be interrupted by a mixed diet, or by giving 100 to 120 grammes of carbohydrate a day, or if a similar addition be made to the unbalanced diet of only protein and fat, the acetonuria stops surprisingly quickly. Even during the day on which the change of diet is made the acetone in the urine may sink to a few centigrammes, as in G. Satta's case above. The values invariably reach the normal in two days at most.

In view of the peculiarities in the acetonuria of inanition already indicated, it would serve no useful purpose to consider the details of its behaviour in chronic malnutrition. The underfed person may be sick or sound, but whether his excretion of acetone bodies is large or small depends only upon the composition of his diet, and is uninfluenced by the degree or the duration of his malnutrition. Most persons who take but little food, either of their own free will or in accordance with medical orders, consume a relatively large amount of carbohydrate. Hence one very rarely finds aceto-acetic acid, and still more infrequently β-oxybutyric acid, in the urine of people who are making up only one-half or even only two-fifths of the heat-supply they need by the food they consume. The same is true of the urinary NH_3, and the acetone in their urine is rarely more than 1 or 2 decigrammes in the day.

Having made a great number of experiments upon patients of every

had not been able to take any food at all. No acetone was present in the urine. Brugsch explains this by the absence of fat (as a source of acetone bodies), the tissue requirements being obtained from protein. From the protein disintegration it was calculated that the total exchange amounted to 140 to 210 calories per day (5 to 7 calories per kilogramme). Was this result due to a gradual wontedness to a deficient carbohydrate intake? Further investigations are required before hypotheses are permissible.

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kind in my wards, I am forced to contradict Waldvogel's statement (185) that the presence of a positive $FeCl_3$ reaction, β-oxybutyric acid, and a high NH_3 value, always indicate a notable degree of underfeeding [von Noorden (186)]. The significance to be attached to these signs in any particular instance depends upon the nature of the case. In illnesses of short duration, such as acute gastritis, pneumonia, diphtheritic angina, etc., the presence of acetone or diacetic acid in the urine does not prejudice the prognosis. In more protracted disorders like typhoid fever, septicæmia, pulmonary tuberculosis, and chronic gastric or intestinal disease, the discovery of aceto-acetic or β-oxybutyric acids in the urine should be taken by the physician as a sharp warning to attend most carefully to the patient's diet. He must not rest satisfied with the supposition that the diet is perhaps adequate, but somewhat lacking in carbohydrate. The carbohydrate is, of course, deficient, but in actual practice a deficiency of carbohydrate is invariably associated with a well-marked and even critical insufficiency of the whole dietary. These considerations, of course, do not hold good in special cases such as dyspepsia and diabetes mellitus, in which special reasons for the limitation of the carbohydrate exist.

(*h*) *Protein.*

During acute starvation protein is often found in the urine, though mostly in minute quantities. With Cetti and Breithaupt albuminuria had already appeared in the first week, and in some observations of my own a marked cloud of albumin was precipitated in the urine on boiling after two or three days of fasting. Koranyi (155) remarked it only after the twentieth day; Ajello and Solaro (187), and E. and O. Freund (26), were unable to find it until quite the later stages of the fast. Such albuminuria can be referred at once to impairment of the kidneys' nutrition; possibly, too, autochthonous poisons injure the renal tissue. Describing a case where albuminuria was accompanied by the passage of renal casts, Nebelthau (21) questioned whether poisoning by acid might not cause the phenomenon. Personally I think this is improbable, for one often sees diabetic patients who show no trace of albuminuria, although their urine may for weeks and months have been rendered highly acid by aceto-acetic and β-oxybutyric acids.

I once observed a case where only traces of albumin were found in the urine during three days of fasting. On the fourth day broth and four raw eggs were taken; marked albuminuria followed, and lasted for sixteen hours. Next day a full mixed diet was ordered, but the albumin did not return; nor did it come back again a few days later, when broth and seven raw eggs were given. This case appears to me to prove very clearly that the renal epithelium can be injured by starvation.

As clinical experience shows, a moderate degree of chronic underfeeding does not commonly lead to the appearance of more albumin in the urine than may be present normally. It is quite otherwise with marked and protracted malnutrition, such as is met with in œsophageal stenosis or hysterical hyperemesis. Here albuminuria, transient or lasting, is the rule, and careful examination under the microscope will

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not fail to discover casts. L. Popow (188) records a case of œsophageal stenosis in which albuminuria occurred whenever the narrowing allowed no food at all to pass; from time to time dilatation could be effected, and then the urine became free from albumin.

Lussana and Arslan found peptone (deutero-albumose or histone ?) in the urine even after two or three days of fasting. They compare the peptonuria of starvation with that seen during involution of the uterus. But the methods employed by both of these authors do not make it sufficiently certain whether they had to deal with peptones or with albumoses. And it is at any rate questionable whether the disintegration of the organs in starvation is comparable to the processes of autolysis that make play with the puerperal uterus.

(*i*) *Sugar.*

Mild glycosuria has been seen in a few fasting experiments, particularly by E. and O. Freund (26). But Succi, whom they were observing, passed no sugar at all in an earlier experiment [Luciani (13)], and no more than the normal amount of reducing substance was to be found in the urine of Cetti and Breithaupt (1). Numerous experiments of my own prove that during short fasts of three or four days glycosuria is undoubtedly absent, even when 120 to 240 grammes of sugar have been taken, in the form of solution, on the fourth and fifth days of fasting. As I stated years ago [von Noorden (190)], the limits up to which carbohydrate can be assimilated are not diminished in man during acute starvation, although in many animals they are—Hofmeister's "starvation diabetes" (191). In cases where positive results are maintained in opposition to the negative definitely proven above, it may not be out of place to consider whether glycuronic acid has not been confused with sugar. It is known that acetone can combine with this acid, producing the so-called "acetone diabetes" (192), and that a large amount of acetone circulates in the tissue-juices during starvation. Further, H. Thierfelder (193) has shown that if suitable substances are at hand the starving organism can form and excrete glycuronic compounds as readily as when it is fully fed.

In my clinique we have never succeeded in producing alimentary glycosuria by the exhibition of 100 to 120 grammes of glucose in ill-nourished patients, even when they were in the last stages of bodily decay and emaciation. Persons who have been inadequately nourished for a long time while wandering about the country have often exhibited spontaneous or alimentary glycosuria during the early days of their stay in hospital. But in such cases of "vagrants' glycosuria" [G. Hoppe-Seyler (194)] the cause must lie at the door of other injurious influences rather than at that of starvation; the misuse of alcohol is particularly to blame [J. Strauss].

(*k*) *Toxicity of the Urine.*

During Succi's fast at Naples in 1892, G. Ajello and A. Solaro (187) investigated the toxicity of his urine by C. Bouchard's method. Injecting the urine into the vascular system of rabbits, they found that the toxicity

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was increased, particularly in the case of the urine secreted during the night. The objections that I raised against this method in the past [von Noorden (196)] are now shared by many, and it is unnecessary to go into the experiments further here, for they prove nothing. (Additional information will be found in the physiological section, also in the chapter on Diseases of the Kidneys.)

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CHAPTER II

OVERFEEDING

By CARL von NOORDEN.

Translated by R. W. Marsden, M.D., M.R.C.P.

One of the most important and most intricate tasks which falls to the lot of the physician at the bedside relates to improvement in nutrition, whether it be to restore a person previously badly nourished and weakly to his maximum state of nutrition and strength, or to replace the material which has been lost by disease. In either case our object is the building up of fresh tissue. In accordance with the importance of this task, the metabolic changes which occur in dietetic cures, in the regeneration which follows starvation and underfeeding, and in convalescence from a previous disease, deserve the most careful study. It will be convenient to deal first with the conditions which are met with in ordinary feeding, and then to treat briefly of the special circumstances which arise during regeneration and convalescence.

1. The Energy Exchange.

By the term "overfeeding" is understood the administration of food in such a quantity as to provide more energy than the needs of the body require. It is a matter of indifference whether the excess takes the form of albumin or of some oxidizable substance free from nitrogen. In my text-book on "Pathology of Metabolism" (1893) I have, amongst other things, expressed my views that the collective store of energy represented by the food which is provided in excess of the needs of maintenance—after the withdrawal of a slight loss (about 6 to 7 per cent.) spent on the increased work of digestion—takes the form of an addition to the body substance, and that no further increase in heat production is occasioned by such overfeeding. The investigations of E. Pflüger (1), M. Rubler (2), A. Magnus-Levy (3), N. Zuntz (4), B. Schöndorff (5), and G. Koraen (6), tend to show that this contention cannot be completely maintained, since variations in the type of food which is taken in excess yield quantitatively different results.

When fat is in excess, even if it be in very large amounts, almost the whole energy arising from such excess passes into tissue substance. According to the calculation of N. Zuntz (4), averaged from all his investigations, with an addition of 100 grammes of fat, 97 to 98 grammes were

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utilized in increasing the body-weight. The small remainder serves for the necessary expenditure of energy on digestion and absorption.

With an excess of carbohydrates the circumstances are not so favourable. N. Zuntz estimates that on an average the energy represented shows a loss of 10 per cent. for digestive purposes, and that with coarse kinds of bread it is considerably higher. Moreover, the change from carbohydrate into fat is not effected absolutely without loss of heat [Rubner (7), Zuntz (4)]. Theoretically, for instance, in feeding pigs 100 grammes of fat should be produced out of every 240 grammes of starch flour, or out of 270 grammes of glucose, 90 grammes being withdrawn for the energy necessary for the digestive process. Practically, however, Meisal and Strohmer (8), in the best results obtained by them hitherto, found the increase in fat about 30 to 35 per cent. less than the theoretical calculation led them to expect. M. Bleibtreu (8) obtained similar figures in feeding geese on carbohydrates.

Again, the results are different when the excess over what is required for maintenance is composed of nitrogenous substances. Working with entirely different methods, E. Pflüger, M. Rubner, A. Magnus-Levy, and G. Koraen have shown themselves in absolute agreement, and have demonstrated that under these circumstances there is an augmentation of the processes of oxidation, oxygen being taken up and carbonic acid given off in a degree which far exceeds what one would have expected from the requirements of the digestive processes. In feeding animals with a rich meat diet Rubner obtained values representing a daily transformation of energy which exceeded those in accord with the food necessary for maintenance by 30 or 40 per cent. and more. In man there is never any need to consider such unusual amounts, because, being omnivorous, he can only replace from protein a comparatively small portion of the food ingested. Even in cases with the maximum increase of albumin the exchange of energy spread over the twenty-four hours will not exceed that met with in a mixed diet by more than 20 to 25 per cent.

Closer study led Rubner (2) to distinguish two effects as the result of feeding on albuminous substances. He found that—

1. The primary effect of a meal rich in albumin is an increase in the oxidation processes, which passes off in about eight to ten hours [Magnus-Levy, Koraen].

2. Under certain circumstances, however, the continued use of a diet rich in albumin leads to a long-continued increase in the consumption of energy, which lasts so long as the excess of albumin remains high. This increase in the waste of energy rises more quickly in accordance with the addition of albumin. Thus for every addition of about 1 per cent. for the albumin the corresponding increase in the consumption of energy is about 2 to 2½ per cent. (the so-called secondary increase of energy transformation from feeding with albumin [Rubner]).

Though differing essentially from each other in their explanation of the occurrence, Rubner (2) and Pflüger (1) are yet in agreement that the secondary exacerbation in the exchange of energy produced by excess of albumin only follows in such cases when an increase in the albuminous constituents of the body is brought about by that and by some other

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constitution of the food as a whole. Whilst Pflüger regards the addition of albumin as the exclusive cause of the increased transformation, and expressly states that the variation in heat production of the body is directly proportional to its amount of nitrogen-containing body substance, Rubner, without wholly denying this connection, seeks a causation rather in an active specific influence of the albumin upon the cells. Experiments which show that when the albuminous addition is associated with an excess of carbohydrates and fat considerable increase in heat production does not occur, constitute for him a decisive and also important practical proof of his contention. In such instances the transformation is indeed augmented, but only gradually, and in accordance with the increase in body-weight.

From the statement just made it is possible to make important deductions with regard to the choice to be exercised in feeding. Sometimes we consider whether the composition of the food can exert any influence on the relationship of the increase of fat to the increase of flesh, and estimate the elements of the food by which we can best guarantee an excess of calories beyond the needs which form the basis of such diet. From this point of view it appears that albumin is least suitable since, along with a low calorific value, the necessary oxidation processes must be considerably increased for its combustion ; thus very little of the surplus calories, which result from the excess of albumin, are left at the disposal of the system. Much better results are obtained by the use of carbohydrates, which, both experimentally and practically, have shown themselves to be the best elements of food-stuffs. Still, for the reasons already mentioned, at least one-fourth of the store of energy contained in the excess of carbohydrates is lost on the way from the stomach to its final storage as fat in the fat depots. The conditions are most favourable in the case of fat. Very little expenditure of energy is required on the part of the digestive organs, and the fat is stored as such almost without any loss of energy. In practice it is still customary to avoid making full use of fat for feeding purposes, and as a rule to prefer carbohydrates. I have, however, on several occasions shown that this view ought to be relinquished, and that—when certain pathological conditions of the stomach and intestine can be excluded—large and even enormous quantities of fat are very well tolerated, with results which can be scarcely attained, much less exceeded, by an abundant exhibition of carbohydrates [von Noorden (9)].

Finally, I must mention the claims of alcohol in feeding. As is shown elsewhere in this book, a very small portion of the energy it represents is uselessly lost. Not only is it burnt up, but during the process of combustion it spares a certain amount of other non-nitrogenous substances. The oxidation of 100 grammes of alcohol prevents the destruction of about 77 grammes of fat, and these may be stored in the tissues as a reserve in the form of fat. It is, however, only in certain limited circumstances that the high nutritive value of alcohol may be made use of for feeding purposes, since its toxic action on individual organs, and on protoplasm in general [K. Miura (10), amongst others], contra-indicates its extended use. The increase in the exchange of

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calories following the fattening of the body-tissue depends on the two following factors:

1. The increase in the amount of protoplasm disintegrated forms the most characteristic feature. After the work of E. Pflüger and his pupils, it seems to me now especially necessary to bring the metabolic changes into relationship with the quantity of protoplasm, as I have done in various places in my text-book on the "Pathology of Metabolism," since, despite all the connections which doubtless exist between the transformation of energy on the one hand, and the body-weight and development of surface area on the other [E. Voit (11)], there is no doubt that in individuals of equal size, and with an approximation to identity as regards surface development and such conditions as rest, exercise, external temperature, etc., the quantity of active and disintegrating protoplasm is determined by the exchanges of energy, etc. Size of body and weight only form a standard in individuals of a medium state of nutrition, so that, these excepted, it may be taken that a certain amount of protoplasm disappears for the loss of a certain amount of weight. The conditions are, however, different in the case of such an increase in weight as that with which we are at present dealing. When large quantities of fat are put on, as happens usually in every form of feeding (81), the body accumulates material which adds to its weight, but which hardly at all contributes to the energy exchange.

As the result of this inclusion of ballast, the balance of energy based upon the body-weight falls, as a rule, in individuals who are being overfed. Numerous experiments in men and animals have shown this balance to be smaller per kilogramme of the body-weight in obese individuals. I may cite as an example the values for CO_2 obtained by A. Magnus-Levy in normal and in obese women (the numbers are averages):

Height.	*Oxygen utilized per Minute.*	*Oxygen utilized per Minute and per Kg.*	*Oxygen utilized per 150 Cm. of Height in a Minute.*
Cm.	C.c.	C.c.	C.c.
151	200·6	4·09	199·2—normal (12).
154	252·4	2·71	249·0—fat (13).

That an addition of flesh (*i.e.*, an increase in protoplasm) augments the transformation of energy is shown, as already mentioned, by the experiments on animals conducted by Pflüger and Rubner. Certain observations by Zuntz seem to me to be even more important and more interesting. By systematic muscular exertion continued through many days and weeks, such as the marching of fully-equipped soldiers, many of the persons subjected to experiment became thinner, lost both weight and fat, but gained a considerable addition of nitrogenous material. The muscles were developed and strengthened by the exercise, whilst when the period of exertion was over the exchange of calories was higher than before, an increase in the protoplasm being the causal factor [Zuntz, Zuntz and Schumburg (15)].

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2. The increase in the actual size of the body, independent of the formation of protoplasm, necessitates an increase in the consumption of energy. Individuals of heavy weight require a greater expenditure of energy in order to move and raise their limbs, etc. This refers not only to movements of the whole body, but to those of particular parts; evidence is yielded by a study of the metabolism of rest, an increase in the work of the heart and of the respiratory muscles occurring in obese persons. Thus, the stout women, the subjects of Magnus-Levy's experiments, utilized 25 per cent. more oxygen than the women of a moderate state of nutrition and of equal size (see table, p. 65). Augmentation of the exchange, with increase of body-weight, is seen also in another observation made by Magnus-Levy (12). During a period of eight weeks, continuous examinations of the gaseous exchanges were instituted in a chlorotic girl. During this time the weight increased 4 kilogrammes.

Date.	*Oxygen utilized per Minute and per Kg.*	*Total Oxygen utilized per Minute.*	*Weight.*	*Hæmoglobin Content of Blood.*
	C.c.	C.c.	Kg.	Per Cent.
31·12–20·1	4·18	180·5	43·2	25
24·1–8·2	4·3	182·7	45·3	49
13·2–25·2	4·18	193·6	47·2	72

The successful feeding, and not the coincident raising of the hæmoglobin content of the blood, was here apparently the sole cause of the increase in the oxygen utilized, since by other experiments it has been sufficiently proved that the respiratory interchange of gas rises with a diminishing concentration of the blood rather than the reverse. Moreover, I may refer to the experiment on a dog by Rubner (p. 7), which clearly shows the influence of the body-weight on the transformation of energy.

By far the most comprehensive experiment was conducted by my former assistants, L. Mayer and F. Dengler (see table, p. 67). It extended over three months. Almost every day the minimal oxygen metabolism was determined in a fasting condition, whilst large additions of albumin and calories led to a considerable increase in weight and the storing of enormous quantities of nitrogen. Details of the addition of nitrogen and calories are contained in the table, p. 74.

The increase in the oxygen utilized corresponds to the extraordinary increase in weight and the surprisingly large augmentation of nitrogen, and leads one to doubt whether the food consumed really produces a corresponding increase in the living protoplasm. For the 370 grammes nitrogen added about 11 kilogrammes of muscular tissue must be calculated theoretically. When reckoned for each kilogramme of the body-weight, it is seen that the consumption of oxygen diminished during the course of the feeding. This is the consequence of the addition of fat, and agrees with known facts already mentioned.

Even to-day it is just as necessary to institute comparative examinations of this kind on the oxygen utilized and calories changed in con-

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ditions of low and later of good nutrition in the same person as it was eleven years ago, when I made the same demand in my text-book on the "Pathology of Metabolism." The few observations made upon the period immediately following that of extreme starvation (Cetti and Breithaupt) cannot be accepted for the ordinary circumstances of feeding, in which the composition of the body only changes slowly. Our knowledge is somewhat more minute concerning exchange of energy in persons convalescing from severe acute febrile diseases. This subject will be considered later.

Period.	*Date.*	*Weight in Kg.*	*Addition of Nitrogen.*		*Amount of Oxygen in C.c.*	*Amount of Oxygen in C.c.*
			Per Period.	Total.		
			Gm.	Gm.	Average per Minute.	Average per Minute per Kg.
1	Nov. 14-30, 1904	56·0	0	0	222·4	3·987
2	Dec. 1-11, 1904	56·0–57·7	+58·57	+ 58·57	226·1	3·930
3	Dec. 12-19, 1904	57·7–59·7	+44·3	+102·87	225·2	3·818
4	Dec. 20-27, 1904	59·7–61·3	+59·5	+162·37	—	—
5	Dec. 28, 1904, to Jan. 4, 1905	61·3–63·5	+69·1	+231·47	228·3	3·646
6	Jan. 5–13, 1905	63·5–65·5	+76·9	+308·37	242·1	3·717
7	Jan. 14-17, 1905	65·5–66·5	+30·6	+338·97	238·7	3·609
8	Jan. 18-21, 1905	66·5–67·5	+26·4	+365·37	240·9	3·576
9	Jan. 22-31, 1905	67·5–69·5	+ 5·6	+370·97	234·1	3·373
10	Feb. 1-10, 1905	69·5–69·0	−12·0	+358·97	233·5	3·393
11	Feb. 11-21, 1905	69·0–69·3	−12·4	+346·57	235·9	3·408

Sometimes it is still impossible to set up definite quantitative relationships between the addition of protoplasm and the increase in the transformation of energy. The usual estimation of the addition from the difference between the amount of nitrogen intake and output does not here suffice. Even under the still questionable acceptance (see later) that all the retained nitrogen in overfeeding may be really referred to the albumin accumulating in the body, it must yet be remembered that a large portion of this albumin is not active cell-protoplasm, but circulates in the blood and in the tissue fluids. What part this free albumin takes in the utilization of energy is quite unknown. When Rubner (16), from short experiments on animals, calculates that for every 1 per cent. increase in body substance the transformation of energy rises about 1·5 to 2·5 per cent., and when Schoendorff (5) reckons that for a cat every kilogramme of the nitrogenous tissue of the animal's body requires an exchange of 70·95 calories, it must not be forgotten that these figures have been obtained under conditions of nutrition too unusual for application to human metabolism. They only indicate the direction in which metabolism trends when a change in the amount of albumin is taking place. They do not yield any definite basis for the estimation of the actual quantities concerned. In the present state of our knowledge, therefore, the following statements appear to be probable :

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1. Every increase in the amount of protoplasm increases the energy exchange.

2. An increase in weight, due to increased intake of fat, also increases the energy exchange.

3. With the ingestion of further quantities of albumin the energy exchange often rises independently of the increase in protoplasm, probably as the result of a peculiar irritative action of the food proteins on the active cells, the exact nature of which is unknown [M. Rubner (2)].

The conditions which obtain in convalescents demand special consideration. As yet they have only been studied during recovery from severe febrile diseases (typhoid fever and pneumonia). I shall deal with the question briefly, since it is discussed in greater detail in another portion of this work (Fr. Kraus, "Metabolism in Fever"). After exhausting acute febrile diseases, which had led to a loss of albumin from the body and to loss of weight, Svenson (17), in the first days after the fever had disappeared, found very low values for the oxygen utilized and the carbonic acid given off (experiments during fasting). The oxygen utilized fell at this period, in a case of a twenty-four year old female convalescent from typhoid fever, to 1·40 and 1·77 c.c. of oxygen per kilogramme per minute (35·5 kilogrammes weight).[1] Svenson and Fr. Müller consider the lowering or prolongation of metabolic activity here shown as an evidence of exhaustion. After a few days, however, the exchange of energy rises, and in the following first to second weeks reaches values which exceed the normal by about 30 to 50 per cent. The metabolism of the convalescent at this period simulates that of the child, which, calculated on the body-weight, has a much more active exchange of energy than the adult. According to R. Tigerstedt and K. Sondén (18), the energy exchange of the one to twelve-year-old boy is to that of the adult as 164 : 100. If, despite the much more active processes of combustion, the convalescent increases in weight, and puts on considerable quantities of flesh, this has its foundation in the fact that the taking up of

[1] I cannot pass by these figures and conclusions of Svenson without mentioning that they must sometimes be accepted with certain reserves. Of the three cases of typhoid fever in question (Cases 1, 2, 4. Svenson), one (Case 2) did not show any fall in the energy exchange at the beginning of convalescence; in another (Case 4) the fall is so slight that the difference does not deviate from what one so often meets with in the patient who makes his first attempt at a respiration experiment. Case 1 alone is remarkable, and, if correct in every respect, convincing. Yet, after the fever has disappeared, the following results appear:

On the second and third days, 111·3 c.c. CO_2 (average per minute).
On the fourth and seventh days, 54·5 c.c. CO_2 (average per minute).
On the eighth day, 123·9 c.c. CO_2 (average per minute).
On the eleventh, thirteenth, and seventeenth days, 158·4 c.c. CO_2 (average per minute).

These values, calculated for about 35·5 kilogrammes of body-weight, are on the upper limit of the normal. What causes me to point out as possible and probable faults in the first four determinations, especially the third and fourth, is the enormous difference in the CO_2 on the seventh and eighth days of convalescence (60·8 c.c. and 123·9 c.c. !). It is almost incredible that the metabolic activity should within twenty-four hours have experienced such a complete change as to attain its correct expression in a doubling of the amount of CO_2. In view of these remarkable figures, fresh experiments are called for.

In a recent work Richter (19) reports on a respiration experiment upon a debilitated female patient at the time she was again being fed up. The values for O_2 and CO_2 were, respectively, 4·8 c.c. and 3·76 c.c. (per kilogramme and per minute)—that is, at the upper limit of the normal.

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nutriment is still more decidedly raised than the energy exchange. According to Svenson, a food intake equal to 60 to 70 calories per day and per kilogramme is not unusual in the convalescent. Even values of 80 to 90 calories have been attained. During the period of the marked putting on of albumin and fat the respiratory quotient rises considerably, as has been also already noted in feeding experiments in animals [M. Bleibtreu (8)], and its magnitude may exceed 1. This is just the reverse of what is met with in starvation when the respiratory quotient sinks abnormally. The marked sensibility and greater tendency to disintegration of the regenerating protoplasm shows itself in the fact that after the ingestion of food, as well as after muscular exertion, the percentage increase in the energy used is higher than in healthy persons.

Svenson found all these peculiarities in the metabolism of convalescents to be more marked after typhoid fever than after pneumonia, this being dependent probably on the greater and longer continued losses, and on the more extensive antecedents of degenerative changes in the tissues of the typhoid fever patient.

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2. Feeding with Flesh and Feeding with Fat.

It is now necessary to discuss the distribution of the nitrogen-containing and nitrogen-free substances in the tissues during overfeeding. That the amount of tissue fat can be increased no matter how the con-

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stituents of the food are changed is a well-known fact which it is hardly necessary to mention. Theoretically, the conditions of fat may be indefinitely raised by continued overfeeding. A limit is fixed only by the ultimate functional incapacity of the intestine and by the harmful effects on vital organs, particularly the heart. Through feeding a person may be practically suffocated with his own fat, and fat people do, in fact, often undergo this fate. Usually, however, by feeding it is only sought to bring about a certain maximum condition of nutrition. However important a certain richness of the body in fat may be from the medical point of view, the object aimed at in overfeeding is that the albumin of the body shall be also increased, since the augmentation of the latter alone indicates additional power and capacity. Many go so far as to allot a therapeutic value only to the increase in the amount of albumin, and totally deny the utility of putting on fat. This is going too far, and indicates theoretical prepossession rather than a sufficient observance of clinical facts. Experience with men and animals has taught that flesh-feeding gives rise to various quantitative, though probably not fundamental differences, dependent on the presence or absence of certain favourable conditions of the body apart from the food. Previous starvation or underfeeding, the stage of convalescence after illnesses, and the normal growth of the body, are instances of these factors. In all these cases the tissues are eager for albumin, and freely take up albumin from the food in order to again build up fresh protoplasm. The peculiarities which arise therefrom will be discussed later. The immediate question which at present concerns us is whether, and to what degree, the putting on of flesh can be attained by overfeeding when such favourable factors are absent—that is, in the case of a previously well-nourished adult person. The amount of nitrogen retained is taken as a measure, even though it is by no means certain that this is equivalent to the accumulation of albumin, or even to accumulation of flesh (see below). Observations on this point are not very numerous. They may be classified as follows :

1. Experiments in which only the amount of non-nitrogenous materials serving as sparers of albumin were increased.

2. Experiments in which only the intake of albumin was increased.

3. Experiments in which both albumin and the non-nitrogenous food were increased.

The experiments of the first group, so far as regards really accurate figures, have been carried out under my direction.

Time.	*Body-weight.*		*Daily Nutriment.*			*Calories.*	*Calories per Kg. per Day.*	*Daily Retention of Nitrogen.*
	Commencement.	End.	Nitrogen.	Fat.	Carbohydrate.			
	Gm.	Gm.	Gm.	Gm.	Gm.			Gm.
Previously, 6 days	59·0	59·4	14·8	151	192	2,575	43·5	−0·402[1]
During feeding, 15 days	59·4	62·5	15·4	227	425	4,285	70·0	+3·30[1]
Previously, 6 days	90·0	88·0	20·4	150	246	2,930	32·5	+2·17[2]
During feeding, 12 days	88·0	89·9	20·1	150	323	3,250	37·0	+3·23[2]

[1] Krug (1). [2] Dapper (2).

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Further determinations (for method, see original papers) showed the following additions of weight, flesh, fat, and water :

	Krug.	*Dapper.*
	Gm.	Gm.
Weight	+3,100	+1,900
Flesh (nitrogen × 29·4) ..	+1,455	+1,170
Fat	+2,254	+ 281
Water	− 609	+ 449

In both cases the nitrogen retention was as active at the end as at the beginning of the experiment. Krug calculates that in his case 7·46 per cent. of the utilizable increase of nutriment (that is to say, of its caloric value) took the form of albumin, and 92·54 per cent. as an addition of flesh. In Dapper's case the corresponding figures were 35·5 and 64·5 per cent. A comparison of the two experiments shows that the absolute daily addition of nitrogen was almost identical, although the excess of calories in Krug's was much greater than in Dapper's experiment. Moreover, Krug's experiment might alone be considered as perfectly free from objections, since in Dapper's, despite the small number of calories given, the nitrogen increase occurred in the first period—an indication, therefore, of previous insufficient nourishment and incomplete albumin intake. In this way the increase of nitrogen in the first period, as well as the relatively large amount of flesh put on, when contrasted with fat put on, is satisfactorily made clear. Krug's reliable experiments show that with an excess of carbohydrates, along with a very marked increase of fat, considerable augmentation of albumin of the body also takes place, and Dapper's experiment shows at least that small additions of carbohydrates can, under certain circumstances, substantially favour the accumulation of albumin. Whether the same result might be achieved if the excess of calories had arisen from fat, instead of from carbohydrates, must remain an open question. There are no feeding experiments on human beings which demonstrate this with certainty. The fact long known from experiments on animals, and established for man also by my pupil, B. Kayser (3), and later by E. Landergren (4), that fat, if it represents carbohydrates in isodynamic quantities, spares albumin less than carbohydrate does, is not applicable at this juncture. Similar investigations by Tallqvist (5), as well as two experiments published by my former assistants, M. Kaufmann and L. Mohr (5), point to the fact that in overfeeding with large quantities of fat the putting on of albumin is not less than that met with when carbohydrates form the preponderating part of the excess of food. In both experiments the subjects were women in a moderate state of nutrition, and before the period of feeding they had for some time received a plentiful supply of rich food. During the feeding period itself the non-nitrogenous elements consisted of fat to the extent of

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three-quarters to four-fifths of the caloric value (much butter and cream).

Time.	*Daily Amount of Nitrogen given.*	*Calories given.*		*Body-weight.*		*Daily Accumulation of Nitrogen.*
		Daily Total.	Per Day and Kg.	Commencement.	End.	
	Gm.			Kg.	Kg.	Gm.
11 days	21·5	4,244	74	57·2	—	+3·18
7 ,,	18·4	5,270	92	—	62·0	+4·89
5 ,,	17·8	4,016	70	56·5	—	+3·82
5 ,,	17·06	5,324	80	—	57·7	+5·85

The experiments of the second group teach that, under certain circumstances, a considerable nitrogen addition can be attained by only raising the amount of albumen given. As an example, the following experiment of K. Bornstein (6) may be cited. An addition of nutrose to a diet in which the intake of non-nitrogenous material was always the same was made from the fifth day onwards :

Days.	*Nitrogen Intake per Day.*	*Nitrogen Output per Day.*	*Nitrogen Retention per Day.*
	Gm.	Gm.	Gm.
1–4	14·9	14·23	0·67
5–8	21·9	18·99	2·90
9–12	21·9	21·09	0·80
13–18	21·9	20·16	1·74

A similar result was obtained in Bornstein's (7) second experiment, as well as in two experiments conducted by M. Kaufmann (8) in my department—to the important points of which I shal lagain return—and as regards individual periods, in the long-continued experiment by Lüthje (9).

These observations are, to a certain extent, in opposition to numerous old experiments by Voit and others, according to which, with a specific increase in the albumin administered to well-nourished animals, there is nitrogen retention during the first days, but after a short time the disintegration of albumin equalizes its intake. The third period of M. Dapper's (2) experiment shows that this may be the case in men, and that the circumstance noted by Bornstein has no claim to general validity. When he added 40 grammes plasmon to the food in the second part of the experiment, the difference between the nitrogen intake and output increased from the first. The albumin exchange, however, soon approximated to the amount given, so that in the period of nine days an average balance of + 2·55 grammes nitrogen was only attained, a quantity less than that noted in the previous period without the addition of plasmon. This is completely in accord with the teaching of Voit.

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The same results appear[1] in a third experiment by Bornstein (10).

Days.	*Nitrogen Intake per Day.*	*Nitrogen Output per Day.*	*Nitrogen Retention—Nitrogen accumulated per Day.*
	Gm.	Gm.	Gm.
1–4	12·58	12·45	+0·13
5–9	19·78	16·97	+2·81 (60 grammes plasmon added).
10–14	19·78	19·33	+0·44

It has still to be discovered why the albumin-feeding, consisting of an increase in albumin, is successful in one case [Lüthje, Bornstein, M. Kaufmann], but not in others [Dapper, Bornstein].

Unfortunately all experiments conducted hitherto on man are too short to demonstrate whether, with a continuance of this form of albumin-feeding, the body can be enriched in its albumin content. The first experiments by Lüthje allow the surmise that the albumin implanted in the body by the particular form of nutriment is only maintained by continued overfeeding with nitrogenous and non-nitrogenous food.

In the more recent experiments by Lüthje and Berger (9) the results were a little more favourable. Of 67·7 grammes nitrogen which were accumulated during a feeding period of ten days, and of the 2·5 kilogrammes increase in weight, there remained 33·79 grammes nitrogen and 0·6 kilogramme in the tissues when the subject of experiment returned, during a subsequent period of ten days, to moderate amounts of food (about 1 to 5 grammes of albumin daily, and about 35 to 36 calories per day and per kilogramme). This modest result is certainly not very satisfactory. It characterizes and at the same time caricatures certain kinds of so-called "feeding cures," whose temporary and immediate success threatens to bring rational methods also into disrepute. As a clinician having an unusually large experience in the subject of nutrition, I must, as I have stated elsewhere [von Noorden (11)], warn against the deduction of Bornstein (11) that the usual method of feeding in which non-nitrogenous material plays the chief part should be discarded, and that we should strive to make the body richer in albumin and stronger merely by increasing the amount of albumin given. Since in the last decade numerous preparations of albumin have been exploited, I see many patients who, on their own account—supported by the advertisements of manufacturers—or as the result of medical instruction, have added large quantities of nutrose, plasmon, tropon, sanatogen, roborat, etc., to their ordinary daily food, with the intention of strengthening themselves. The practical result, however, was of the most meagre description, and

[1] From this experiment Bornstein himself quite incomprehensibly draws different and totally unauthorized conclusions. All that the experiment shows is that, precisely in accordance with the old teaching of C. von Voit, an accumulation of albumin, brought about by increasing the albumin of the food, soon reaches its limit. In addition, the experiment proves in an excellent manner that in "albumin-feeding" the sulphur of the albumin molecule is retained as well as the nitrogen.

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not to be compared with the lasting gain which the same persons obtained subsequently from a typical feeding cure.

To the third group belong, so far as healthy individuals are concerned, the experiment of Lüthje (9) (partly in co-operation with Berger). In a patient convalescent from typhoid fever, by an enormous increase of albumin and non-nitrogenous material soon after the termination of the disease, Lüthje attained a marked retention of nitrogen, and he repeated this experiment some months later when the man was apparently in a normal state of health.

Days.	*Nitrogen per Day.*	*Calories per Day.*	*Nitrogen—Total Accumulation.*	*Nitrogen Retention.*	*Weight in Kg.*	*Calories per Kg. and per Day.*
	Gm.		Gm.	Gm.		
8	30·8	3,326	+ 4·64	+ 0·58	82·7	40
6	30·9	3,326	+14·80	+ 2·47	83·1	40
5	41·7	4,720	+28·25	+ 5·65	84·3	56
5	42·5	4,720	+32·75	+ 6·55	85·4	55
5	61·0	6,035	+69·19	+13·84	87·6	70

Lüthje observed a similar result in a parallel experiment on a woman. Unfortunately investigations of the metabolism after a return to ordinary diet are wanting. According to an earlier observation by the same author (11), after a return to the normal intake of albumin and calories large quantities of the retained albumin undergo disintegration.

Finally, the feeding experiment of L. Mayer must be mentioned. The associated values for oxygen utilized have already been given (see p. 67).

No.	*Duration (Days).*	*Daily Nitrogen.*	*Daily Calories.*	*Nitrogen Retention per Day.*	*Weight at End of Period.*	*Calories per Day and per Kg.*
		Gm.		Gm.	Kg.	
1	3	14·7	2,183	−0·7	56·0	39
2	11	30·8	3,147	+5·3	57·7	54
3	8	34·1	3,270	+5·9	59·7	54
4	8	40·2	3,422	+7·4	61·3	56
5	8	41·0	4,182	+8·6	63·5	66
6	9	42·0	4,451	+8·6	65·5	68
7	4	31·5	4,695	+8·8	66·5	70
8	4	42·0	4,451	+6·1	67·5	66
9	10	22·5	3,768	+1·4	69·5	54
10	10	15·9	3,080	−1·2	69·0	45
11	11	18·5	2,661	−1·1	69·3	39

In this experiment the tissues of a man aged forty-two years, who was previously in a good state of nutrition, gained 371 grammes nitrogen within seventy-two days.

These records indicate that there are various ways in which the store

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of albumin in the body may be raised. It is, however, only in connection with the manner and extent of the addition that we possess sufficient information, and not with the at least equally important question, how far one can push the accumulation of albumin, and how the retained albumin ultimately behaves when the individual, after the overfeeding, resumes his ordinary dietary (see below).

From the experiments of Lüthje and Berger (8), as well as the recent one by L. Mayer, it appears that a large portion of the ingested albumin is rapidly excreted, and that another portion remains for a certain length of time in the body, but there do not exist any results which show whether this is a lasting acquisition, and what particular kind of diet ensures the best and most permanent condition. It would be most advantageous, both from a theoretical and practical standpoint, were it possible for this particular type of experiment to be repeated on a broader basis, and made to extend over long periods of time ; unfortunately, however, there are many technical difficulties to be overcome. In the absence of exact experiment, it is necessary to accept the experience of the clinician. For nearly twenty years I have given the most careful consideration to these points. In my opinion, feeding-cures on Weir-Mitchell's old plan, in which the patient is kept in bed for weeks, and, in order to obtain a more rapid increase in weight, all unnecessary exertion avoided, do not afford any grounds for strengthening the muscular powers. By these means obesity, but not strength, is produced. When the muscles are exercised at an early stage in the cure the results are more satisfactory [von Noorden (11)]. That is to say, in the language of the teachings of metabolism, the vital properties of the protoplasm are the ultimate measure of eutrophy of the cells, and not the excess of nutriment.

The gaps which exist in our knowledge of the metabolic processes in man are, to a certain extent, filled in by experiments on animals. Boards of Agriculture have initiated numerous investigations in order to determine the best methods by which cattle can be fed for purposes of consumption. E. Kern (12) concludes that the increase in the living weight of adult animals on a "fattening" diet, after the removal of the wool, depends solely on an accumulation of fat. In animals still growing, also, the "fattening" foods do not markedly increase the putting on of flesh. The experiments of Pfeiffer and Kalb (12) yielded more favourable results when they added exceptionally large quantities of albuminates to the "fattening diet" of the sheep (relation of nitrogenous substance to carbohydrate plus fat, 1 : 2·35). After allowing for the fleece, the daily accumulation of nitrogen in a feeding period of 100 days came to 0·71 gramme to 1·29 grammes. Without the albuminates, although the number of calories given was very high, there was little or no addition of flesh.

Kühn's (12) experiments upon one-year-old oxen—which must be described as the best and most reliable investigations extant—were again less favourable. They showed that an intake of albumin (gluten and meat meal) was not associated with any greater nitrogen retention than an intake of food poor in albumin, but simply increased the protein

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exchange. An increased administration of non-nitrogenous material in the form of carbohydrates led to a slight and continuous nitrogen addition. In general, in the rearing of cattle, the production of an accumulation of flesh by an increase of food, or by special mixtures, has not been possible. Only additional fat has been produced by such means. In order to obtain muscular, fleshy animals, it is necessary only to breed such animals as, from inherited predisposition, show in their individual development the capacity for a marked formation of muscular tissue.

When, in addition to the requirements for nutriment, the organism has a special need for albumin, the conditions for the accumulation of albumin are doubtless very much more favourable than in simple overfeeding.

Moreover, when the food is just sufficient, and even when the amount of albumin and number of calories is insufficient—so long as the underfeeding is not too pronounced—nitrogen is retained; this is much more marked in overfeeding. In all these cases genuine flesh formation can be counted upon, a conception by no means covered by the simple retention of nitrogenous material[1] (see below). These favourable circumstances, which lead to a genuine formation of flesh, take place under certain definite conditions [B. Krug, von Noorden (1)].

1. Flesh formation occurs in the body during growth.

The facts are here quite clear. The growing tissue takes up albumin and other constituents of the food in order to build up the necessary tissue elements. It is a condition and consequence of growth that the tissue-forming elements are less in amount in the excretions than they are in the food. Soxhlet's (13) experiments on sucking calves give clear evidence of the enormous "attraction power" of growing tissue. With the usual average intake the animals retained as follows:

	Per Cent.
Of albumin	68·00
Of total ash	54·30
Of phosphoric acid	74·23
Of chlorine	6·22
Of calcium	98·00
Of magnesium	40·00
Of potassium	22·37
Of sodium	25·31
Of iron	33·30
Of carbon	43·00

Investigations on infants yield essentially the same result (see Vol. III., Metabolism in Childhood). Even with insufficient food the need of the growing body for albumin makes itself felt, the infant retaining nitrogenous substance in combination with sodium salts, whilst it gives up fat [Rubner and Heubner (14)]. Camerer (15) had previously demonstrated this in a long series of experiments which he conducted on his own children. On the ordinary rich diet nitrogen-containing material was invariably retained; it was not until the children reached sixteen and seventeen years that the retention became less prominent.

[1] Compare also the detailed discussion by A. Magnus-Levy in Vol. I.

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2. Flesh is formed during pregnancy and lactation. The maternal organism takes nitrogenous and other tissue-building material out of the food in order to build up the tissues of the child, whether it be in the uterus or by means of the breasts [Stohmann (16), Soxhlet (13), O. Hagemann (17), Fr. N. Schulz (18) for animals; Zacharjewsky (19), Th. Schrader (20), A. ver Eecke (21) for human beings]. If the food is not sufficient to cover the maternal and embryonic needs for albumin, the embryo obtains the necessary material tissue-protein of the mother, the energy for growth on the part of the embryo being greater than the retentive power of the adult body. An observation by Schulz (18), which showed that the entire albumin of a normal, fully-formed young dog originated from the maternal tissues, teaches this fact very clearly, while daily experience indicates a similar process in man. Women who are nourished with great difficulty, and lose flesh during pregnancy, often bear normally developed children. After child-birth, and during the period of suckling, the circumstances are more favourable for the mother, less favourable for the child, since only upon a nutritious diet does the secretion of milk—in other words, the formation of the flesh by the child—remain undisturbed.

3. Formation of flesh takes place in those who are no longer growing, but who are performing a larger amount of work than usual (hypertrophy of muscle during hard work). The fact is quite patent. The increase in the volume of muscle in men and animals accustoming themselves to hard work is a palpable and well-known symptom. In experiments on metabolism also it has been possible to show how much work favours the accumulation of nitrogen [K. Bornstein (7), W. Caspari (22), A. Loewy (23), J. Kaup (24), W. Schumburg and N. Zuntz (25), Pecori (26)]. In the case of adult man this factor might, indeed, importantly contribute to the augmentation of the disintegrating protoplasm, much more important than overfeeding in whatever form. By overfeeding, obese individuals, not athletes, are produced. With systematic muscular exercise the nitrogen retention may even take place when the nutriment has not covered the total requirements, and to such extent has led to a loss of fat [Zuntz and Schumburg].

4. Flesh formation occurs in every case in which the body has suffered a loss from starvation, underfeeding, or disease, and again returns to a more satisfactory state of nutrition.

It has been shown that the recuperative powers of the organism with regard to nitrogen retention come into evidence when the need for calories is not abundantly satisfied. Under these circumstances, the tissues have the preference when the food is increased. Naturally the conditions of the accumulation are most favourable when an excess of food is combined with the efforts at regeneration on the part of the organism. These are the circumstances which must frequently be dealt with in practice when a feeding cure is indicated.

Hitherto exact experiments on the aspect of metabolism have been almost exclusively made on convalescents from acute febrile diseases, such as typhoid fever and pneumonia (see the following chapter) [Puritz, Dünschmann, H. Benedict and N. Suranyi, Lüthje, Svenson, A. Albu,

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P. F. Richter (26A)]. The following figures, when compared with those obtained by feeding healthy individuals, show how markedly the activity of the accumulation of nitrogen is increased in convalescents :

Days of Convalescence.	*Nitrogen in Food.*	*Calories in Food.*	*Calories per Kg.*	*Daily Accumulation of Nitrogen.*	*Weight.*	*Observers.*
	Gm.			Gm.	Kg.	
15–27	18·69	3,188	55	+6·54	56·5–69·4	Benedict and Suranyi (typhoid).
28–36	20·54	3,238	54	+7·69	59·4–51·4	
37–47	18·63	3,324	55	+7·56	61·4–64·3	
3–13	21·3	3,216 (average)	about 56	+5·92	about 56	*Ibid.* (typhoid).
14–17	21·92	4,327	73	+7·33	57·5–58·5	—
18–25	17·04	4,215	71	+5·00	58·5–59·8	—
26–34	28·29	4,589	74	+9·82	59·8–63·7	—
35–42	27·17	3,598	56	+5·56	63·7–65·2	—
43–62	27·24	2,912	44	+4·86	65·2–68·1	—
3–13	18·20	2,775	50	+3·62	55·0–56·0	von Noorden, 1893, unpublished observation (typhoid).
14–23	18·20	2,775	48	+4·05	56·0–59·4	—
24–33	18·20	2,775	46	+5·87	59·4–61·0	—
4–10	19·10	2,180	42	+3·82	52·0–52·8	—
11–18	19·10	2,380	45	+4·93	52·8–54·1	von Noorden, 1893, unpublished observation (after severe sepsis).
19–23	20·20	2,600	48	+3·14	54·1–56·0	—

Comparing these figures with those of B. Krug and others (see above), the accumulation of nitrogen in convalescents is much more marked, in spite of the lowered or only just equal calorific values of the food. Neither from these nor from other experiments on metabolism in convalescents does it appear that the free administration of albumin favours the accumulation of nitrogen to any great extent. A more likely connection is the relationship between the number of calories given and the amount by which the nitrogen of the body is enriched.[1]

In the forms of underfeeding associated with the habitual taking of food in insufficient amounts (especially in poor women), in chronic

[1] I do not understand how Benedict and Suranyi conclude from their experiments that the overfeeding alone, and not the special conditions of convalescence as regards their need of albumin, brought about the marked nitrogen retention. Their experiments show clearly that the convalescent more readily puts on nitrogen than does the healthy individual. Rosenfeld (27) also shares the view that the eagerness of convalescents, to take up nitrogen must be referred to overfeeding exclusively. Amongst other things he argues that an accumulation, far exceeding the state of nutrition of the patient previous to the disease, is produced by a continuance of abundant food. That is, of course, a thoroughly fitting observation from a clinical point of view. Still, it must be remembered that most patients, for whom we possess exact records, have certainly not entered upon the disease in a maximum state of nutrition and an optimum condition of protoplasm. The majority were in circumstances unfavourable as regards nutrition, the careful provision of an abundant supply of nutriment being first made during their convalescence. They then learned how to eat and to diet themselves sufficiently, very often retaining this practice afterwards. It may indeed happen that individuals previously spare gradually become stout after illness. I have elsewhere dealt in detail with this cause of adiposity in reference to the conditions of nutrition following pregnancy and lactation [v. Noorden (28)]. This does not, however, sustain Rosenfeld's contention.

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gastric diseases, and in chronic diseases in which the appetite is diminished, such as tuberculosis, the accumulation of nitrogen is less than during convalescence from acute febrile diseases, even when there is a high caloric intake. In the latter condition the contrast between the destruction of albumin through toxins during the pyrexial state and the exertions towards reorganization on the termination of the fever is exceptionally well defined.

In a wasted girl Ewald and Dronke (29), by marked overfeeding (the value in calories was not accurately calculated), produced an accumulation of 83·72 grammes of nitrogen in two months (about 1·4 grammes daily).

In a feeding experiment by Bleibtreu (30) on the Weir-Mitchell plan, nearly 190 grammes nitrogen were retained in forty-seven days (about 1·4 grammes per day). The albumin content of the food was unusually high (about 178 grammes per day).

In a patient with chronic disease of the stomach (gastric catarrh and subacidity) von Noorden found (31):

Days.	*Nitrogen in Food.*	*Calories in Food.*	*Calories per Kg.*	*Nitrogen taken up Daily.*	*Weight.*
	Gm.			Gm.	Kg.
3	14·1	1,347	33	+0·69	40·5–41·0
3	16·8	1,825	44	+2·0	41·0–
3	17·2	1,986	48	+1·40	41·0–41·5
3	17·3	2,230	56	+2·30	41·5–
8	19·9	2,363	54	+3·90	41·5–45·0
7	18·0	2,231	50	+4·10	45·0–45·4
6	18·1	2,414	53	+3·40	45·4–46·0

Some observations from F. Hirschfeld's (32) experiments may be included here (Observations 2, 3, 4):

Days.	*Nitrogen in Food.*	*Calories in Food.*	*Calories per Kg.*	*Nitrogen taken up Daily.*	*Weight.*
	Gm.			Gm.	Kg.
21	19·0	4,141	74	1·64	56·0–60·5
21	23·0	4,405	92	1·55	48·0–51·8
21	19·2	4,386	88	3·30	49·0–54·1

It is interesting to consider how the accumulation obtained through feeding is divided between nitrogenous material and fat. The calculation only gives approximate values, since accurate estimates of the whole interchange of nitrogen were not made in any of the experiments[1] (see table, p. 81).

[1] In the table the values represent the averages of previously-mentioned experiments. I follow the method of calculation used in Krug's work. In convalescents and in individuals who were themselves the subject of experiment an exchange of 40 calories was taken; in the remaining persons, who led a life free from every exertion during the experiment, an exchange of 35 calories per day and per kilogramme was assumed. For the work of digestion and the increase in the transformation of energy 15 per cent. was subtracted from the difference between the actual numbers of calories given and the calculated requirements. Every increase of 1 gramme of nitrogen was valued at

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A collective survey of the experiments here recorded, and a consideration of those not here detailed, permits the following conclusions:

The nitrogen gain is absolutely, as well as relatively to the simultaneous putting-on of fat, greatest in those convalescing from severe acute diseases. It is less, but still considerable, in patients who were in a condition of inanition before the feeding was begun, and whose body-weight was consequently far below the average.[1]

The smallest nitrogen gain—absolute as well as relatively to the fat put on—is seen in individuals who were already well nourished before the experiment commenced. Observations such as those in which the albumin output and the caloric intake rose to an unusual height are the only deviations from this rule [Lüthje (11), Lüthje and Berger (9), F. Dengler and L. Mayer]. It has already been pointed out that only a portion of the gain remains in the body after a return to the ordinary conditions of nutrition. As a rule, even with considerable additions of food, a daily accumulation of 2 to 2·25 grammes cannot be exceeded. As shown by Bornstein (10), such an addition can be attained only by increasing the albumin, and even then a standstill is soon reached [Bornstein (11), Dapper (2)]. It is not known how long the end gain can be maintained by a persistent increase of non-nitrogenous substance within reasonable limits, or through a similar augmentation of all the elements of nutrition. Moreover, it is only therapeutical experiences, and not exact experiments, which teach that the gain in albumin and fat resultant upon systematic feeding can be permanently maintained, unless fresh illness, poor external circumstances, or an irrational method of living, disturb the patients afresh.[2]

34·8 calories [1 gramme of animal albumin in a swollen state ; 5·567 calories, von Rechenberg (33)]. After the product from the nitrogen accumulated, multiplied by 34·8, is subtracted from the excess of calories, the number of calories remaining indicate the fat added. This calculation differs in part essentially from those introduced by the authors themselves. But although my method of calculation only gives approximate values, I believe it to be the only correct one. Benedict and Šuranyi have used a method which was quite inadmissible.

[1] Amongst the experiments extant, two of the observations of F. Hirschfeld contained in the tables alone form an exception to this. The nitrogen gain was strikingly small. More detailed information concerning the previous nutrition is wanted. It must be assumed that it was unusually rich in albumin.

[2] I must here insert an observation bearing on practice. Complaint is often made that feeding-cures have no utility, since the increase in weight obtained soon disappears again. According to my experience, this complaint is only correct when feeding-cures are combined with complete bodily rest and absolute isolation of the patient (as in Weir-Mitchell's original method), and when the feeding consists, by preference, of a heaping-up of the carbohydrate. One week, at latest, after the commencement of the feeding the patient should be allowed to perform muscular exercises. These should be increased from day to day, and at the end of a further two weeks must equal the average amount of muscular work. Massage is useless. Muscular work favours the accumulation of albumin. Increase in weight is hardly less than with perfect rest, because the greater disintegration is abundantly compensated by a better appetite and a larger intake of food. Further, in feeding, preference should be given to fat over carbohydrates. Larger quantities of carbohydrates than 300 to 400 grammes daily are, after a time, not well tolerated. Where the patient, however, under the compulsion exercised in an institution, takes in the large amounts of food necessary to permit of the carbohydrates being used on removing the compulsion, the feeding-cure is often terminated by a period of marked loss of appetite, in which much of the carefully acquired body-weight is lost again. On the contrary, the high calorific value of fat allows a combination of high food value with small volume, and the reaction to a period of marked loss of appetite is much less frequently seen [v. Noorden (34)].

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Observers.	*Food Nitrogen.*	*Excess of Calories.*	*Of the Calories in excess there were used in the Body—*				*Remarks.*
			For Storage as Albumin.		For Storage as Fat.		
			Absolute.	Per Cent.	Absolute.	Per Cent.	
	Gm.		Gm.	Gm.	Gm.	Gm.	
Krug ..	15·4	1,537	115	7·46	1,422	92·54	Healthy and well nourished.
Kaufmann and Mohr	21·5	1,906	111	5·80	1,795	94·20	Healthy; moderate state of nutrition.
	18·4	2,775	170	6·10	2,605	93·90	
Kaufmann and Mohr	17·8	1,683	133	8·00	1,550	92·00	As before.
	17·0	2,830	204	7·20	2,626	92·80	
Lüthje ..	30·8	367	20	5·40	347	94·60	Healthy.
	30·9	355	86	24·20	269	75·80	
	41·7	1,505	197	13·10	1,308	86·90	
	42·6	1,472	228	15·50	1,244	84·50	
	61·0	2,524	482	19·10	2,042	80·90	
Benedict and Suranyi	18·7	790	227	28·70	563	71·30	Convalescent from typhoid.
	20·5	733	268	36·60	465	63·40	
	18·6	738	263	35·60	475	64·40	
Benedict and Suranyi	24·3	830	206	24·80	624	75·20	Convalescent from typhoid.
	21·9	1,723	255	14·80	1,468	85·20	
	17·6	1,594	174	10·90	1,420	89·10	
	28·3	1,868	342	18·30	1,526	81·70	
	27·2	893	193	21·80	700	78·20	
	27·2	258	169	65·50	89	34·50	
Von Noorden	18·2	489	126	25·90	363	74·10	Convalescent from typhoid.
	18·2	387	210	54·30	177	45·70	
	18·2	316	204	64·50	112	35·50	
Von Noorden	16·8	342	70	20·50	270	79·50	Stomach affection; badly nourished.
	17·2	468	49	10·50	419	89·50	
	17·3	662	80	12·10	580	87·90	
	19·9	720	136	19·00	584	81·00	
	18·0	558	143	25·60	415	74·40	
	18·1	707	118	16·70	589	83·30	
Hirschfeld	19·1	1,795	57	3·20	1,738	96·80	Badly nourished.
	23·0	2,273	54	2·40	2,219	97·60	
	19·2	2,197	115	5·20	2,082	94·80	

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The increase in weight aimed at in feeding-cures are naturally in the first place, dependent on the amount of added food. Out of a large number of feeding-cures I have calculated the following average values :

Excess of Food.	*Weekly Increase in Weight.*
Calories.	Gm.
500 to 800	600 to 1,000
800 ,, 1,200	800 ,, 1,200
1,200 ,, 1,800	1,200 ,, 2,000

There are many deviations from these average numbers, due more especially to the varying amount of water contained in the body. When a healthy man whose body has the normal admixture of elements (albumin, fat, water, salts, etc.) submits to a feeding-cure, scarcely any change appears as regards water in the relative composition of his body. This was, for instance, evidently the case in the experiments of B. Krug, Lüthje, and Berger. It is quite otherwise when insufficient food intake or illness precedes the experiment. In the usual feeding-cures which concern wasted, badly-nourished persons it is evident in most cases that during the first weeks of the feeding the body-weight rises in an exceptional manner, much more than appears possible from the most liberal calculation for the flesh and fat accumulated. The difference can only be explained by the water taken up by the blood and tissues. Then, frequently, in the third or fourth week, despite the giving of calories in equal or increased amount, the rise in weight comes to a standstill, or, at any rate, takes place very slowly. At the same time diuresis increases. The accumulation of fat and albumin during this period go on undisturbed, but the body is poorer in water. Other types also occur. When nutriment is somewhat plentiful, chlorotic patients often excrete very large quantities of water, so that, despite the overfeeding, the weight does not immediately rise [v. Noorden (35), E. Romberg (36)]. The same condition is met with in persons convalescing from severe febrile diseases [Svenson (26)]. Unfortunately the fluctuations of water in the body in the various forms of overfeeding have not, as yet, received much attention, so that all calculations of tissue gain which are based on changes in weight are very uncertain [Lüthje (9), M. Kaufmann (37)].

Thus, the difficulties in these calculations in their relations to the given amount of excess of calories, increase in weight, accumulation of nitrogen and fat, are not yet surmounted. As I have already accentuated in my text-book on "The Pathology of Metabolism" (p. 181), and as F. Müller (38) and his pupil Svenson (26) have recently urged, the human body is not disposed to permit an increase under all circumstances, especially an increase in nitrogen. After typhoid fever, for instance, there generally follows a gain in albumin, and the same obtains after severe hæmorrhage. With certain infections and intoxications, however, this occurs with great difficulty, so that, by overfeeding, obese but muscularly weak individuals result. Certain forms of tuberculosis and syphilis come under this heading.

Up to now we have only discussed the accumulation of nitrogen from overfeeding. What becomes of the accumulated material ? Is the nitro-

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genous substance saved, added to the albumin already in the body as an equivalent fresh store of albumin, endowed with vital properties identical with the old? Upon this point many views are current.

In the first place, the possibility must be admitted that a part of the albumin is destroyed, but that the nitrogenous products of destruction are insufficiently excreted. A retention of nitrogen then occurs without an accumulation of albumin—as, for instance, in kidney affections. When feeding with an excess of albumin, this must be allowed for. In a dog weighing 22 to 23 kilogrammes, after abundant feeding with flesh, B. Schöndorff (39) found 40 grammes nitrogen accumulated in the tissues in the form of nitrogenous water-free extractives, and 20 grammes nitrogen which was not precipitated by phosphotungstic acid (chiefly urea). If such unusual conditions of nutrition are ignored, larger accumulations of nitrogenous cleavage products in the body do not appear to occur [M. Gruber (40)].

With regard to the large quantities of nitrogen which can be accumulated by feeding with a plentiful supply of albumin [Pflüger (41), Lüthje (11), Dengler and L. Mayer], and considering the difficulties of demonstrating that this increase is an enrichment in albumin, E. Pflüger speaks of an "unknown feeding material," which may probably be an albumin richer in amido-acids. Lüthje adopts the same view, and insists that it must be a substance which contains a smaller percentage of water than the ordinary lymph and tissues. This conclusion, based upon the balance of water in feeding-cures, seems to me quite uncertain. In any case, a conception only partially manifest cannot be bound up with the notion of the "unknown feeding material."

Pflüger's theory of the "unknown feeding material" has many points of contact in common with the teaching of C. von Voit (32), who introduced the idea of the "circulating albumin" into the physiology of metabolism. According to Voit, there is in the first place only an increase of the albumin in the body lymph from overfeeding with albumin, or from the albumin-saving action of fat, and carbohydrates. Much later, and only under special conditions, an increase of the tissue-albumin takes place. Voit derives the difference especially from the fact that the freshly-ingested albumin for the most part undergoes destruction again more readily, so that one diminishes the albumin or the albumin-saving elements, whilst the original stock of albumin in the body (the "organic albumin") is much more capable of withstanding these influences. This information, obtained on dogs, is also confirmed for man by Lüthje's experiments. My own hypothesis was not fundamentally different from the teaching of Voit. I suggested that the albumin compulsorily saved by overfeeding does not merely stay in the blood and lymph (circulating albumin [Voit]), but is itself deposited also in the cells as "reserve stock"—analogous to the excess of glycogen and fat—thus occasioning a supply of albumin to the individual cells (43). Röhmann (43) adopts the same view. The change in this direction in the teaching of Voit is more necessary to-day than eleven years ago, since one has experienced in the meantime what enormous quantities of albumin may be temporarily forced upon the body through overfeeding, without the composition of

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the blood changing in a corresponding degree. From comparative investigations on the muscle fibres in starvation, and when the muscles are well nourished and hypertrophied through exercise, we have learnt that the individual cells (especially the muscle fibres) may vary much as to the amount of lymph, and consequently alter their volume [Statkewitsch, Loeb, Loewenthal (44)]. In the adult body, as stated by Virchow in his "Cellular Pathology," an increase in volume of the individual cells seems to be exclusively concerned, and not a genuine multiplication of cells as contrasted with the growing body, in which it may be observed that an active mitosis follows immediately upon abundant feeding. In what form the albumin is taken up by the cells is at present undecided. If one adheres to what is apparently irrefutably accepted—viz., that the albumin from feeding deposited in the cells[1] has a different constitution and a different biological significance to the remaining cell protoplasm—then the various granules of albumin[2] occurring in the cells—for the analytical study of which we are especially indebted to P. Ehrlich (44) and his pupils—may be brought to mind. The individual single parts which fill the cell space might be considered as endowed with different biological powers. Some constitute the active disintegrating factor governing the transformation of energy; others form passive material, which is taken up by the phagocytic cells as "reserve albumin," the amount depending to a large extent on the coincident circumstances of nutrition of the whole body, and undergoing marked fluctuations. Rapid destruction may follow quickly upon sudden increase, just in the same manner as was demanded by C. von Voit for his "circulating albumin." I might, indeed, designate the "circulating albumin" [Voit] or "reserve albumin" [von Noorden] as food albumin, but not as genuine tissue food [Fleischmast]. The latter term should only be used when a fully-formed albumin accrues which possesses all the biological properties, more especially the like energy of disintegration and the like power of continuance as the ordinary cell albumin. Bornstein (10) alone takes up the stand that these properties are immediately acquired by all ingested albumin. His reasons, however, are by no means satisfactory, especially when founded on the conclusion unjustifiably drawn by Bornstein from practice, that the giving of much albumin aids in bringing about the "eutrophy" of the cells, and compels an addition of protoplasm. Daily experience should, indeed, warn against such a conclusion. We do not by any means find the individuals of the greatest muscular power and with the most plentiful stock of protoplasm in the class of people who consume the largest amounts of albumin and flesh, but in those who,

[1] In my text-book on "The Pathology of Metabolism" I have spoken of the "reserve of albumin" as "dead-cell inclusions." This expression was awkwardly chosen, and has led to interpretations of my hypothesis [Bornstein (6)] which were far from my own way of thinking. My sole intention was to bring into prominence the contrast between active protoplasm and passive cell contents, and I made use of a far too drastic expression in adopting the idea that the passive "reserve of albumin" does not take part in the biological functions of the cells. Naturally one cannot, in a strict sense, speak of "dead albumin" in the living body.

[2] In order to prevent misconception, I may expressly mention that I do not in any way consider the recognised neutrophile and eosinophile granules as food albumin. They are much more likely to be specific cell products.

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with a measured and moderate amount of albumin, through the accustomed, energetical work endow the muscle with magnetic power equivalent to the albumin.

At my instigation, attempts have been made to bring forward the proof of genuine flesh-feeding by examining whether the accumulation of inorganic salts takes place coincidently with the accumulation of nitrogen.[1] The question is very intricate, but the following considerations may be cited :

If the increased administration of nitrogen means albumin-feeding, then, at any rate, besides nitrogen, sulphur must also be retained, since this is an integral part of the molecule of albumin. Bornstein (10) has recently shown that in nitrogen-feeding sulphur is accumulated, the relationship of nitrogen to sulphur being, in fact, the same to the average composition of albuminous bodies. This is an important discovery, and it might render material aid in thoroughly removing the unsatisfactory conception of " unknown feeding material."

When sulphur-containing albumin but no mineral elements are retained, then blood and lymph must first be considered as the situations for its retention. Recently F. Müller has demonstrated that the percentage composition of the blood as regards albumin frequently falls so low in badly-nourished and anæmic persons that 100 to 200 grammes or more of albumin may be necessary to again raise the whole volume of blood to its normal protein content. This event, occurring in convalescents from exhausting diseases, in chlorotic individuals, and probably also after previous underfeeding, does not necessitate any, or only a slight, retention of mineral elements. The real question, whether albumin-feeding leads to an increase in the " circulating albumin," in the sense of C. von Voit, is not decided by these considerations, since proof is wanting that there is accommodation for as much fresh albumin in the juices of a fully-nourished, healthy man as has been actually added to the body by feeding-cures. Although there are no exact determinations, it seems impossible to raise the albumin percentage of lymph beyond a certain maximum. In the meantime, it has been noted that mineral substances are frequently retained with the albumin, and where this is the case it forms decided evidence against the accumulation of " circulating albumin." It may be, however, safely inferred that a portion of the ingested albumin always remains in the blood and lymph channels.

When elaborated albumin is retained, but no mineral elements, a feeding of cells with " reserve albumin " may occur [von Noorden]. It is, of course, more likely that albumin will be accompanied by mineral elements when it is taken up by the cells.

When elaborated albumin is retained, together with mineral elements, there is evidently an entrance of the albumin into the cells. It cannot, however, be decided as yet whether that which enters into the cells is a phagocytic prey (reserve albumin) or a geniune increase of protoplasm. A relatively marked retention of phosphorus itself indicates, with some

[1] Concerning the question of nitrogen-feeding, albumin-feeding, and flesh-feeding, see the excellent contribution by M. Kaufmann (45) and the work of Lüthje and Berger (9), also that of Magnus-Levy in the Physiological Section.

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degree of probability, an increase in the nuclear substance. Of all inorganic elements, the most careful attention has, in fact, been given to phosphoric acid, since qualitatively and quantitatively it has the most far-reaching connections with the albuminous constituents of the cells. The experiments upon this point may be classified in the following groups :

1. Röhmann (47) and his pupils found in animals, and Cronheim and Müller (48), Ehrstrom, and L. Büchmann observed in men, that albumin in organic combination with phosphorus (casein preparation, yolk of egg) produces an accumulation, not only of nitrogen, but also of P_2O_5. Experiments by O. Loewi (49), which consisted in feeding men and animals with nuclein, tell the same story ; and L. Büchmann proved that by the addition of lecithin similar effects on the accumulation of phosphorus can be obtained as with the phosphor-containing albumin bodies.

2. Even when, according to the experiments just cited, the organic combinations of phosphorus are most favourable to its accumulation, still, the body does not lack the ability to absorb and assimilate inorganic phosphates, and store them in combination with albumin. This was shown by A. Keller (50) in a growing infant. In adults, as seen in Röhmann's experiments, the assimilation of phosphorus is manifestly more difficult. L. Buchmann conducted an experiment in my clinic giving albumin free from phosphorus [Edestin] and inorganic phosphates. Nitrogen was retained, but not phosphorus. Later, E. Koch, at my request, repeated the same experiment (not yet published), and, in agreement with Keller, found the nitrogen gain accompanied by that of phosphorus. In any case, by contrasting these experiments, it is evident that, according to the circumstances under which the experiment takes place, and according to the momentary state of nutrition of the individual, at one time only albumin and at another time organ-forming mineral, is accumulated from an abundant supply of material containing both nitrogen and phosphorus. This is dependent less upon the chemical nature and formation of the material given than upon the existing condition of the body, since, even when the phosphorus is administered in an organic state, the body sometimes retains the nitrogenous substance and rejects the phosphorus. This is demonstrated by the experiments of Röhmann when feeding with casein, and by those of H. Vogt (51) when giving nuclein.

3. The same experience is repeatedly noted in ordinary feeding experiments. My own pupils, M. Kaufmann and L. Mohr (5), M. Dapper (2), as well as, recently, Lüthje and Berger (9), have determined the balance of calcium and magnesium, as well as that of nitrogen and P_2O_5. After the P_2O_5 necessary to satisfy the retained alkaline earths had been deducted, it was found that the quotient $N : P_2O_5$ often accurately agreed with the relationship which generally obtains in the tissues. On other occasions, however, the quotient fluctuated markedly above or below.

4. The unique experiment which M. Kaufmann published from my clinic seems to me especially important. When he added large quantities of an albumin containing little phosphorus (white of egg) to a constant diet, the body retained considerable quantities of phosphorus in addition

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to the nitrogen contained in the extra food. The same occurrence was repeated in an observation made by M. Dapper (2).

From all these experiments the most important point to recognise is the great selective power which the body possesses in regard to food-stuffs given in excess. It is only within certain limits that the action of the food-stuffs *en masse* acquires any influence over the accumulation of tissue-forming material. Moreover, from the accumulation of phosphorus, which is more often undetected, it is evident that this may be occasioned by albumin-feeding, and not by tissue-feeding, using this term in the sense I have defined. It cannot, however, be decided from any of these experiments whether, in any of those cases in which an accumulation of phosphorus accompanied the accumulation of nitrogen, the material absorbed into the tissue substance is " reserve albumin " or a genuine addition of protoplasm.

I am of opinion also that one cannot proceed much further in this direction, though I formerly considered it possible. A better explanation of the significance of feeding with nitrogen may be expected from experiments on respiration. If it should be found that the transformation of the energy of the body—as inferred by Pflüger (52) from his experiments —rises and falls in an exact proportion to the increase of its store of albumin, then it would be quite wrong to doubt that the overfed albumin became genuine protoplasm. It must still remain undecided whether the augmentations in the transformation of energy previously discussed, which are found after inordinately raising the albumin intake, and with an increasing body-weight, are to be explained in this sense ; this doubt is intensified by the observations specified by Rubner (53), in which there was no augmentation of the transformation of energy despite an increase in weight, and, more especially, despite a considerable accumulation of nitrogen [Voit and A. Korkunoff (54)].

The question whether a genuine putting-on of flesh by the adult organism may be obtained through any form of overfeeding must, therefore, be left unsolved.

In the experiment by Dengler and L. Mayer, which I have already reported, the increase in the oxygen utilized was very small, and did not stand in any relationship to the amount of albumin accumulated. This does not mean that the nitrogenous material ingested was endowed with the same biological properties as the older tissue protoplasm.

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CHAPTER III

FEVER AND INFECTION

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The title of the present chapter, Fever and Infection, so happily chosen by von Noorden, avoids the difficulty of drawing a hard-and-fast line between, on the one hand, those phenomena produced in the organism by infection, and in particular the manifold disturbances of metabolism, which are directly and exclusively associated with febrile rise of temperature, and, on the other hand, those manifestations which are due to infection properly so-called—that is to say, to the specific infective agent, by which the fever is produced.

In the present section all those alterations of metabolism will be grouped together which are characteristic of the ordinary response to infective agents. By the expression "ordinary response" is meant the general reaction of the organism, as opposed to the local reaction, to pathogenic bacteria. The term "ordinary response" serves also to emphasize the circumstance that the reactive processes in question are more or less common to all forms of infection. Clinical experience, in particular, constantly necessitates comparison of processes of reaction with one another, as a result of which clinical conceptions are formed. Taking its origin out of this practical standpoint, the clinical conception of fever has survived all attacks made upon it. Nevertheless, it is undeniable that clinical teaching has paid too little account of the fact that the symptoms grouped under this term by no means correspond so closely in different febrile infective diseases as is frequently insisted upon. Especially does it appear to me now to be no longer admissible to refer to the clinical course of a febrile rise of temperature in purely general terms. The nature of individual infective processes requires much more elucidation than it has received in the past, for the type of fever is obviously dependent both upon the specificity of the substances which have called it forth, and upon certain defensive powers possessed by the organism and its tissues, which require special investigation in each infective process, simple or mixed. Thus, in malaria the type of fever appears to be connected with the biological development of the plasmodia and the formation of swarm spores; in recurrent fever, with the diminution of specific bactericidal substances in the serum, circulating as a response of the organism. It is just as little possible to bring the advantage and disadvantage of febrile rise of temperature under a single

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point of view. Equally cogent considerations and facts are opposed to an absolute uniformity of the alterations of metabolism occurring during the decline of infection.

In addition to metabolic disturbances and a rise, or, it may be, a fall of body temperature, the general symptomatology of infection includes, as is well known, a number of changes affecting the leucocytes and blood (positive chemiotaxis, exudation of leucocytes, acceleration of the lymph-stream, alteration of the amount of total protein or of individual proteins of the blood or bone-marrow, etc.), various lesions of cell structure, as also numerous nervous, cardio-vascular, digestive, hepatic, pancreatic, renal, cutaneous, and other affections.

We set forth with the prevailing view that the general effect commonly produced by infective processes, as also the varied combination of symptoms which characterize each individual case, is due to an intoxication dependent upon bacterial proteins and toxins liberated in the body by microbes, which multiply and are constantly undergoing lysis. The mere presence of proteins and toxins in the body fluids, however, is not enough; their action appears in general to depend upon the fact that they become combined with the living cells of various organs through the agency of specific molecular groups present in the blood (haptophore groups and receptors of Ehrlich). This combination is the pre-condition of toxic action. Susceptibility of the organism to particular diseases, on the one hand, and immunity, on the other hand, regarded as biological processes, are, in the light of modern conceptions of such processes, not fixed functions of the organism, but depend upon manifold physiological and pathological factors; capacity for infection and immunity (which latter, like the toxic effect of bacteria, is provisionally, at any rate, to be regarded as characterized by the presence of chemical substances) are, according to P. T. Müller, whose teaching is here followed, merely different expressions—dependent upon different external conditions—of the complex relations existing between body cells and micro-organisms. We are dealing, in fact, with two extreme cases, differing merely quantitatively, between which every gradation of transition is to be found. Regarded in the light of actual experience, immunity (by which is meant the capacity for resistance to the exciting causes of disease and to the poisons which they produce) and healing processes (that is to say, all processes which limit the intensity and arrest the spread of the organic and functional lesions produced by infective disease, bring the infection to an end, and render recovery of the injured tissues possible) appear plainly as something opposed to infection, yet even purely clinical observation fails to enable a sharp distinction to be drawn between the symptoms of disease properly so called and the biological response resulting in a specific alteration of the original susceptiblity of the organism.

Regarded from this standpoint, the special significance of febrile rise of temperature in the syndrome of infection, with which it is in such close causal relation—in spite of the fact that the existence of chemical poisons produced by micro-organisms and capable of causing a rise of temperature is not yet established—does not appear to us to lie in the circumstance that it forms a leading symptom which is pathognomonic

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nor that it forms the central point of a group of symptoms, and is in direct connection with other important functional disturbances (of metabolism, respiration, circulation, etc.), or, again, that it exercises a deleterious influence upon the organism. The significance of the rise of temperature resides rather in its relation to immunity—whether, in fact, it merely forms an indicator of the onset of immunity, or whether it plays an integral part in its production. An exhaustive account of experimental investigations upon the influence of a high body temperature upon the course of infective processes set up in animals is here out of place, since such investigations scarcely permit of an application to the naturally-occurring infective diseases of man. The course of the development of infection and that of the elevation of temperature are, as Wassermann has rightly emphasized, in man quite different from those obtaining in such experiments. We have as yet no conclusive ground for assuming that an elevation of temperature of itself hinders the growth of bacteria in the body or brings about their destruction. Elevation of temperature is one of the commonest accompaniments of infective processes, but the same excitant of disease by no means produces fever in every case. Whether it does so or not depends, apparently, sometimes upon accidental circumstances—as is illustrated, for example, by erysipelas—sometimes upon the localization of the infective focus. We shall see later that the dictum of Wassermann—that "we know experimentally that the production of these (defensive) substances, as well as the reaction leading to their appearance, invariably commences with fever"—possesses no universal application. Further, the immune reaction is by no means the sole cause of the fever. That it may be in part concerned in the production of fever is quite possible, though clear proof of this is hardly to be obtained. A critical lowering of temperature, produced by timely administration of immune serum, whereby the necessity of producing defensive substances in the body is avoided, can scarcely be regarded as furnishing such proof. Moreover, we have conclusive evidence that, in animals infected with bacteria, additional processes affecting temperature—for example, hæmolysis—occur. Lastly, the artificial lowering of elevated temperature, brought about by antipyretics, does not markedly interfere with the production of immunity. After Baginsky had suggested an inquiry into this point, Schütze, under Wassermann's direction, found that the serum of rabbits into which a virulent typhoid culture had been injected agglutinated in a dilution of 1 in 60 or more; if the animals were at the same time kept for five or six days under the influence of antipyrin administered hypodermically, the immune substances in their serum showed no difference, in point of efficacy and date of appearance, from those found in animals treated with typhoid cultures alone. All these facts render it desirable to give elevation of temperature a special place among the processes constituting the general reaction to infection, and to explain its occurrence by reference to its mode of origin—that is to say, to disturbed heat production dependent upon more or less disordered regulative power. No attempt will, therefore, be made to refer either the general reaction or the group of symptoms constituting fever, to a single factor such as, for example, elevation of temperature or

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some particular quantitative or qualitative disturbance of metabolism. The intoxication produced by infective processes produces most varied fundamental disturbances and defensive processes, some, indeed, interdependent, all of which are conditioned by a common cause.

In this section it is not possible to give more than a curtailed reference to the different kinds of bacterial poisons, and their distribution and localization by chemical means; to toxin analysis; to the complex nature and the properties of bactericidal substances; the normal presence and the source of complement; to the different types and the nature of antibodies; the combination of toxin with antibody; the relation between neutralization of toxin and the production of antibodies—in particular, to the relation between receptors and antibodies according to Ehrlich's side-chain theory; and to the individual types of antitoxic and antibactericidal immunity. The process of immunization will be discussed only so far as it influences the general metabolism of the organism and the composition of the tissues, these being capable of chemical or toxicological investigation, though not of bio-chemical study in the bacteriological sense of the term. Further, the influence of preceding disturbance of the normal chemical condition of the body upon antibody production will be considered.

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1. Albumin Immunity and Nitrogenous Metabolism.

We have attempted to find out such an alteration of metabolism—in particular of protein metabolism—which, in addition to its connection with the process of immunization, is uninfluenced by the temperature of the body, and exhibits the function of defence in its fundamental relation to the mode in which fixation of toxin occurs. In this the modern theory of immunity is freely drawn upon, especial prominence being given to Ehrlich's side-chain theory. As already pointed out, a property common to all antibodies is fixation by means of chemical affinity. Ehrlich brings the assimilation and subsequent oxidation of food-stuffs into the same category as the combination of toxin with cell-protoplasm and the resulting toxic action; the combination with toxin is simply a special instance of the general process of assimilation, toxins possessing haptophore groups similar to those of food-stuffs, and becoming attached in the same manner. The original conception of immunity as a raising of resistance to injurious substances has of late years been superseded, and we now know that widely different poisonous, or, it may be, in themselves harmless, substances of animal or vegetable origin (proteins, ferments) can under certain circumstances become assimilated without being previously acted upon by the secretions of the alimentary canal, and, through the action of the cells of the organism, lead to the appearance in the blood-serum of the animals used for experiment of the same changes which are found in bactericidal and antitoxic sera. The action of immune serum upon bacteria and their poisons being a special case of the above-mentioned general biological process, which is so aptly illustrated by the property possessed by food-stuffs of acting like antibodies, it is to be anticipated that nutritive material, after being taken up by cell-protoplasm, is quickly broken up and oxidized; while, on the other hand, in the case of a toxin, equally with unsuitable or imperfectly prepared nutritive material, the combination between receptor and antibody, or its equivalent, would persist, for a time, unchanged, the cells being unable to deal at once with material to which they are not accustomed.

Ehrlich's conception of a close parallelism between the process of normal assimilation and the action of toxins leads, especially when the production of precipitin by immunization with serum is called to mind, to a closer understanding of the bio-chemical significance of antibodies and immune substance in the wider sense of the term. The investigations of Friedemann and Isaac upon the relation between immune substance and nitrogenous metabolism, carried out in our laboratory, form a logical sequel to the older conception of immunity, and permit of some pertinent analogies, which are well worthy of consideration.

Friedemann and Isaac started with the assumption that assimilation consists in the transformation of foreign protein into protein which is natural to the organism. The labile proteins—adapted as they are for metabolic purposes—which circulate in the body-juices and are present in the tissues, not only are independent of the kind of food taken, but,

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in addition, are specific for the species of animal in question. The required alteration of molecular form (by addition or removal of nitrogen or nitrogen-free groups, or any other means by which change of chemical constitution of the proteins ingested may be effected) naturally manifests itself in the daily nitrogen output, capacity for assimilation being exhibited in increased dissimilation, whereby molecules are produced which are capable of supplying the needs of the organism in respect of the production of energy. The transformation of the protein eaten into new protein within the body takes place in the main in the alimentary canal. The possibility that in many animals the cells lying beneath the epithelium of the alimentary tract preserve their capacity of assimilating foreign protein taken up by the latter cannot be rejected *a priori*. When, however, foreign protein is injected hypodermically, it is possible that these cells, if they no longer possess this power of assimilation, may yet react by producing specific antibodies, so that the possibility that the appearance of immunity represents a process in which body cells resume their function of metamorphosing foreign protein must be kept in mind. When the foreign protein is not at once eliminated by the excretory organs, the initial inability of the cells to assimilate it is indicated by its remaining for a longer or shorter time unaltered in the body. Determination of the total nitrogen output, and its distribution in the urine, teaches us, however, much more of the part played by protein transformation in connection with immunity than does a direct investigation of the fate of the protein injected, if the production of a specific precipitin is the test employed; or, again, than does the output of coagulable protein in the urine after injection.

The experiments of Friedemann and Isaac, which confirm the previous observations of Forster and Sollmann and Brown, show, in the first place, that in fasting dogs which have reached a condition of nitrogen equilibrium the subcutaneous introduction of egg-albumin is followed in the course of a few hours, or it may be several days, by the elimination of an approximately corresponding amount of nitrogenous material in a non-coagulable form (more than 80 per cent. being urea), the relative distribution of nitrogen in the urine not being materially altered. The results of four such experiments were as follows:

Amount of Nitrogen injected.	*Amount of Nitrogen (in the Form of Non-coagulable Material) excreted.*
Gm.	Gm.
3·96	4·17
2·18	1·71
1·74	2·79
2·06	2·07

The amount of albumin eliminated in the coagulable form varied from an amount too small to be estimated up to 25 per cent. of the whole. Among intermediate products of protein metabolism, albumoses were recognisable by means of the method employed by Devoto and Ivar Bang when egg-albumin had been injected into the blood. Up to the present, however, amino-acids and polypeptides have not been detected by the naphthalinsulpho-chloride method.

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On immunizing dogs with egg-albumin, Friedemann and Isaac confirmed the observation of Oppenheimer that these animals do not form precipitins. Treated animals behave differently from untreated ones only when special conditions of experiment are adhered to. Thus, if very large amounts of egg-albumin have been repeatedly administered, upon subsequently injecting a fresh quantity the animals react by eliminating an extraordinarily large amount of nitrogen. For example, in one experiment the injection of 1·83 gramme nitrogen was followed by the elimination of 7·87 grammes nitrogen above the amount which, in the absence of injection, would be expected to appear.

Between the dog and the goat a very marked difference was observed, and this may perhaps exist between carnivorous and vegetarian animals in general. As judged by the elimination of nitrogen, the goat rapidly uses up its own albumin when such is injected subcutaneously. On the other hand, if foreign albumin is injected before immunization has been brought about, the nitrogen corresponding to the amount injected is retained. After immunization the amount of nitrogen eliminated, when nitrogen equilibrium has been reached, is increased. The injection of albumin in immunized animals is always followed by a considerable increase of the nitrogen eliminated in the urine, and this increase is much above that which would correspond to the nitrogen introduced by the injection. The increase coincides with the appearance of precipitin in the blood. Moreover, the relationship of the alteration of protein metabolism to immunity is shown by the circumstance that it is specific, in the sense of appearing only after injection of the kind of albumin employed for immunization or of a closely-related variety.

The following experiment by Friedemann and Isaac illustrates this point:

In 1905 a goat weighing 9,650 grammes was treated as follows:

Feb. 3: 5 c.c. egg-albumin were injected subcutaneously.
„ 9: 5 c.c. „ „ „ „
„ 13: 10 c.c. „ „ „ „
„ 17: 10 c.c. „ „ „ „
„ 20: 15 c.c. „ „ „ „
„ 23: 20 c.c. „ „ „ „
„ 25: 20 c.c. „ „ „ „

On this day, before the injection, a marked precipitin reaction was obtained. On March 9 the following experiment was commenced:

	Quantity of Urine.	*Total Nitrogen.*	*Urea.*	*Urea Nitrogen.*	*Coagulable Nitrogen.*	*Non-Coagulable Nitrogen.*	*Remarks.*
	C.c.	Gm.	Gm.	Per Cent.	Gm.	Gm.	
9	960	3·30	—	—	—	—	—
10	460	3·80	3·20	84·3	—	—	
11	780	3·29	2·81	85·4	—	—	Injection of 100 c.c. egg-albumin = 1·75 grammes nitrogen.
12	700	4·82	—	—	0·48	4·34	—
13	385	6·35	5·27	83·1	Trace	—	—
14	105	1·8	—	—	—	—	Death.

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The significance of this experiment becomes clear when it is borne in mind that the nitrogen output in the urine affords a measure of the destruction of albumin occurring; for both dogs and goats were alike in a condition of hunger equilibrium at the time of injection subcutaneously of fully-formed albumin. The nitrogen eliminated during the period of experiment corresponds almost entirely to albumin, and, since the stored-up albumin had already been used up during the fasting period, this albumin must consist, if we disregard for the moment the foreign albumin injected, of body albumin, or, to use Hofmeister's expression, of "stable" albumin. If the albumin were given by the mouth, only a portion would, after absorption, be reconstituted as albumin in the interior of the body, but in the experiment quoted the whole of the albumin injected has to be dealt with as such.

In the dog the albumin injected behaves like albumin given by the mouth, causing an increase of protein metabolism corresponding to the amount taken in, and to the appearance, in due course of time, of an increase of nitrogen in the urine, just as if the foreign albumin were completely burnt off. (The accompanying output of sulphur has, unfortunately, not been determined.) When we assert, therefore, that it is the albumin injected, which is broken up and burnt off, this assertion is as much justified as a similar assertion concerning albumin given by the mouth. In either case all we know is that a correspondingly increased output of nitrogen is observed. Friedemann and Isaac have shown, further, that a dog fed on a diet rich in fat maintains its nitrogen equilibrium practically unchanged, whether the albumin is administered by the mouth or injected under the skin; in addition, these experimenters succeeded, after long-continued feeding on an exclusively carbohydrate diet, in obtaining the inclusion in the organism, as part of itself, of the whole of the albumin injected. The animal thereby foregoes a source of energy which this albumin offers; this is brought about by the abundance of nitrogen-free food, which protects the albumin injected from the destructive forces of the organism, and leads to its incorporation in the form of nitrogen-containing material. We may legitimately assume that a part of the albumin thus assimilated replaces "stable" body protein which has been used up. On the other hand, it is improbable that the albumin injected is broken up by the body fluids outside the cells of the body, for this would imply the destruction of numerous body cells and the setting free of appropriate ferments. Why should the body cells of flesh-eating animals be more readily called into action than those of the goat? It is highly probable that the urine daily excreted, even when its nitrogen is approximately equal to that injected, includes only a part of the latter, together with nitrogen from other sources; this view is in harmony with the conditions obtaining when albumin is given by the mouth. Certainly the possibility is excluded that a purely toxic destruction of protein, set up by the foreign albumin injected, alone occurs—that is to say, that a simple poisoning of protoplasm far exceeding the momentary protein requirements of the organism takes place, and leads to a discharge of the remains of destroyed cells into the blood-stream, where complete destruction occurs. Such a toxic destruction of protein would

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take place in the second of the experiments of Friedemann and Isaac just quoted, no matter whether, in addition to the albumin injected, carbohydrates were given by the mouth or not. Theoretical considerations seem to render permissible the assumption, based upon the line of thought originated by Ehrlich, that the foreign albumin molecules first become chemically combined with living cell-protoplasm, forming side-groups on the larger protoplasmic molecules, and are then oxidized, and so made use of for supplying energy. A complete division of labour between the cells of the intestinal tract and those of the interior of the body, in respect of the breaking-up of foreign protoplasm, has not taken place in the case of carnivorous animals.

The power of readily decomposing and assimilating foreign albumin within the body which the dog exhibits affords an explanation, in accordance with Ehrlich's theory, of the circumstance that the injection of albumin is not followed by the formation of precipitins. This absence of precipitin formation cannot well be attributed to the lack of suitable receptors. It would rather seem that such receptors are present in the body cells, form during a short period a combination with the foreign albumin, and then resume their uncombined form again.

The behaviour of the goat before treatment and after immunization is not easily to be explained, owing to our imperfect acquaintance with the physiological significance of food-stuffs. In contrast to the dog, vegetable feeders (sheep), according to Pfeiffer and Kalb, become adapted to animal food by merely administering large quantities of albumin by the mouth. Nevertheless, little that is certain is known respecting the significance of the different forms of albumin present in the body, or the manner in which retention of nitrogen in the body is advantageous to the organism. Here we may remark in passing that, in discussing this subject, we adhere, as Magnus-Levy has done in the physiological portion of this work, to Hofmeister's terminology of "labile" and "stable" protein, in order to preserve a non-committal attitude. That the nitrogen retained by the untreated goat is made use of in the body, not in the form administered, but in the form natural to the animal, appears highly probable from the results of the line of experiment adopted by Friedemann and Isaac, notwithstanding the fact that no direct comparison was made between the nitrogen, on the one hand, and the sulphur or phosphorus on the other hand, of the retained food-stuff and of the injected albumin. So far as we are able to judge, the rapid disappearance of antibody from the circulating body fluids indicates that the foreign albumin injected has become combined. A sojourn in the body cells in the form of unorganized labile albumin, on the ground of analogy with the dog, is unlikely. The increased destruction of protein, extending, it is to be presumed, to the foreign albumin injected, is effected in a carefully-immunized animal by means of a specific change of metabolism attended by the appearance of immune body; and it is significant that this is accompanied with characteristic, it may be severe, symptoms of illness and with increased susceptibility to albumin, sometimes leading to a fatal issue. The protein retained appears to represent a special form of cell-included albumin, and, as is well known, Lüthje even regards in this light the albu-

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min administered. For the reasons already given, the altered metabolism, involving more protein than that injected, cannot be regarded as a merely toxic destruction of protein. Friedemann and Isaac, with the aid of Ehrlich's side-chain theory and of data supplied by von Dungern, Pfeiffer and Friedberger, and Bordet, have formed a very definite conception of the way in which immunity leads, in the goat, to the development of the condition, which in the dog is from the first physiological. These observers set out with the assumption that the essential feature of immunity consists in the production of a special side-group in the albumin molecule, this constituting the antibody properly so called. As soon as the antibody combines with the receptor of the albumin injected, it becomes contained within the complex group thus formed, and is thus removed from action as far as the organism is concerned. The amboceptor, produced by immunizing, not only possesses a group coinciding with the receptor of the antibody proper, but, in addition, another group, which is peculiar to the animal from which the amboceptor comes. With any kind of amboceptor obtained from the goat it is possible to produce an anti-amboceptor which will attack all amboceptors of the goat, no matter how they originate. When precipitin is formed, the complex molecule resulting from the combination of foreign albumin with goat's precipitin contains the receptor which is specific for the goat, and can thus be dealt with by the goat, just as its own protein can be dealt with. This saturation of injected albumin with precipitin, of course, does not take place exclusively, or even for the most part, in the circulating fluid. The receptors in the cells attract albumin, and make it part of their substance. Until recently we could only speak of albumin becoming attached to these cell-receptors; now we know from Friedemann and Isaac's investigations that albumin is broken down, and gives rise to urea in the cells of the body. Thus it is seen that the attempt to explain the function of defence in respect of the mode in which injurious substances are fixed by the body cells has not been wholly fruitless. It may well be asked whether it would not be better to characterize the various forms of protein present in the organism, to which so many contradictory names have been given, by reference to the mode of their combination with the protein molecule of living protoplasm.

Since after immunization normal protein is produced out of foreign protein, the question arises, What is the cost to the organism of this transformation, so far as can, in the present state of our knowledge, be ascertained? The characteristic feature of immunity is that it is to a certain extent specific. The former conception of immunity as an exclusively defensive or reparative process is now, however, as has been already insisted upon, considerably modified. The experiments of Friedemann and Isaac tend to show that the immunized animal possesses a greater capacity for breaking up foreign substances than does the normal animal. The accompanying breaking up of the albumin molecule in the living protoplasm, to be subsequently regenerated, is nevertheless not a wasteful process, so long as the groups liberated, which form the antibodies, are not destroyed to an inordinate extent by the digestive and oxidative functions of the organism. In a dog after treatment the increase of nitrogen in

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the urine is, as we have already seen, not necessarily greater after subcutaneous injection than when albumin is given by the mouth. In the goat after immunization there takes place, in addition, a destruction of body-protein, for the increased output of nitrogen markedly exceeds the amount administered. It is not admissible to assume that this increased nitrogenous metabolism falls under Pflüger's dictum, that "increased protein destruction is attended with increased functional capacity, and ensures survival in the struggle for existence," although under other circumstances such an assumption might, in spite of the wasteful character of the process, reasonably be made. The progressive wasting of goats in the course of a lengthened period of immunity is partly to be accounted for by this disturbance of nutrition. Further, the other symptoms of illness, which have long been known and have recently been again emphasized by Wolff, indicate that even so simple a form of immunity as that to foreign albumin implies a profound and severe functional disturbance, not rarely exceeding the capacity of the organism. Exactly how the assimilation of substances which in themselves are not poisonous comes to produce such a lasting injury to the organism is doubtful. Apparently, the cause of this undesirable accompaniment, apart from the inclusion in the destructive process of the liberated groups forming antibody, lies in an accompanying toxic action of the foreign albumin taken up, which far exceeds the so-called "stimulus of combination," and injures the cells of specially susceptible organs, in consequence of the introduction of a toxophore group into the protoplasm molecules. This would constitute a specific toxic intracellular destruction of protein.

The experiments of Friedemann and Isaac do not furnish an explanation of the manner in which immunity is produced by bacterial proteins and toxins—substances which present an analogy to foreign albumin. Nevertheless, it is scarcely to be doubted that the processes above described as occurring in albumin immunization also take part in the production of increased protein destruction in infective conditions.

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2. Increased Protein Destruction as Symptom of Infection: Its Causation and Characters.

Since the investigations of Vogel (1854) and Traube (1855) the increase of nitrogenous metabolism in infective processes in man, and in experimentally induced infection in animals, has come to be accepted as one of the best ascertained facts in the pathology of metabolism. The idea has been later added that in fever more protein is broken up than occurs normally under the same conditions in respect of food.

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The older literature on this subject has been critically compiled by Huppert (1868), and also by Voit in his "Manual." The contributions of Senator (1870) also are memorable in the history of the metabolism of fever. Since then full confirmation of the experience and conceptions of that epoch has been forthcoming.

It is true the extent to which nitrogen is eliminated in infective processes still remains difficult to estimate, for a precondition of such estimation is an unvarying normal metabolism or heat production, and likewise a knowledge of the alteration from the normal corresponding to the period of inanition.

It must be admitted that it is not easy—indeed, it is in many respects impossible—to bring animals into a febrile condition which is strictly comparable to fever affecting human beings for periods, it may be, of weeks or months. Further, it is exceedingly difficult to maintain a marked degree of fever in animals, or to ascertain in advance the alteration of metabolism in different stages of inanition in young animals, because the conditions of the actual experiments to be performed later may be affected thereby. The metabolism of inanition must, in consequence, be assumed to be following its usual course. Nevertheless, in spite of these difficulties, the extent to which nitrogen is eliminated in febrile states is best determined in animals, for such determinations can then be made—(1) during a period of complete starvation, when metabolic equilibrium is easily reached, during which the nitrogen in the urine $\times 6{\cdot}25$ closely represents the amount of protein utilized, while the irregularity of metabolism brought about by refusal of food or imperfect absorption are avoided; and (2) while albumin is being continuously administered in equal daily amounts, so that a nitrogen equilibrium is obtained. The latter observations can only be made upon animals, but in both cases the determination of total metabolism may be combined with an investigation of the daily gaseous exchange without unduly increasing the difficulties of experiment. The febrile diseases peculiar to animals may conveniently be employed for such investigations.

By inoculating the bacillus of swine erysipelas upon rabbits during a period of starvation (and deprivation of water) may be produced a febrile condition lasting two to three days. On the first day no increased output of nitrogen was noted; on the second day in all the animals experimented upon (five in number) the output exceeded the normal by 28·4 to 51·9 per cent.; on the third day the output was increased (only one animal was observed) by a further 18 per cent.

The following is one of May's experiments (rabbit, weight 2,838 grammes):

Commencement of hunger period, 6 p.m., July 20, 1892.

Third day (normal), from 6.21 p.m., July 22, when the rectal temperature was 39·5° C., to 6.1 p.m., July 23, when the rectal temperature was 39·5° C.; 0·3 c.c. of a broth culture of the bacillus of swine erysipelas, diluted 1 in 50, was then injected intravenously.

Fourth day (commencing fever), from 7·40 p.m., July 23, when the temperature was 39·5° C., to 6.1 p.m., July 24, when the temperature was 41·2° C.

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Fifth day (fever marked), from 6.55 p.m., July 24, when the temperature was 41·2° C., to 6.2 p.m., July 25, when the temperature was 40·7° C.

Day of Experiment.	*Average Weight.*	*Rectal Temperature.*	*Nitrogen Output.*
	Gm.	Degrees C.	Gm.
3rd	2·480	{39·2 / 39·5}	1·79
4th	2·378	{39·7 / 41·2}	1·81
5th	2·270	{41·2 / 40·7}	2·45

Stähelin, in a recent important investigation upon metabolism in fever, to which frequent reference will be made, infected dogs with surra, causing very rapid debility. It may be observed that surra, which is caused by a trypanosome, is common in India among animals, and is fatal to dogs and horses, which become infected through mosquito bites, and exhibit an extreme degree of wasting. The dog experimented upon by Stähelin, which was fed upon dog-biscuits, was first brought into a condition of nitrogen equilibrium, and then (June 18, 1903) inoculated subcutaneously with the blood of an animal which had been ill for eight days. The experiment extended over the whole period of the disease. The animal was kept in Pettenkofer's respiration apparatus (calorimeter chamber), and the output of nitrogen, carbon, and water determined. In addition, calorimetric determinations of the food, urine, and fæces were made. Increased metabolism due to muscular work was completely avoided. Urine and fæces were collected outside the calorimeter. In the eight days preceding infection (June 10 to 18) the animal retained not more than 0·15 gramme nitrogen, and exhibited an output of carbon which was 4·45 grammes above the intake. During the following fourteen days the animal, with one exception, took all its food; during the succeeding seven days took part of its food; and during the last four days refused food. The amount of water taken could not be kept constant. During the preliminary period 140 c.c. was found to be sufficient; on the third day after inoculation the amount required to be doubled. The first appearance of illness after inoculation was noticed on June 22 (the period from infection to onset of fever extended from June 18 to June 29). On June 22 the temperature became high, then fell, and on the 26th again became elevated. On June 28 another remission occurred. From thence onwards the dog's condition became worse, and rapid wasting occurred. After June 29 extensive œdema was noted; on July 3, hypopyon; after July 8 the animal could no longer stand. Icterus was next observed, and a further fall of temperature. On July 10, Cheyne-Stokes respiration; on July 12, convulsions. The urine always contained albumin, and on the last six days glycosuria was present. The febrile period is subdivided (in consequence of experimental omissions) into three

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parts : June 24 to June 28, during the latter days a slight error in the determination of CO_2 and H_2O occurring ; a further period, during which only the nitrogen balance was accurately ascertained ; and a third period, from July 5 to July 8, during which nitrogen, carbon, and the H_2O balance were determined. To the febrile stage succeeded the final stage from the 8th to the 12th of July, during which the temperature was subnormal.

The average balances of nitrogen were as follows :

	Nitrogen in Food.	*Nitrogen in Urine.*	*Nitrogen in Fæces.*	*Nitrogen Balance.*
	Gm.	Gm.	Gm.	Gm.
Preliminary period (June 10 to 18) ..	5·67	4·135	1·38	+0·15
Incubation and prodromal period (June 18 to 24)	4·45	4·14	0·82	−0·51
First fever period (June 24 to 28) ..	5·67	5·87	0·98	−1·18
Second fever period	4·37	5·89	0·98	−2·50
Third fever period (July 5 to 8) ..	3·34	5·19	0·71	−2·52
Terminal period (July 8 to 12)	0·45	—	—	−4·7

In the preliminary period, as also in the period from June 18 to 24, nitrogen equilibrium is fairly well maintained. During the first fever period the dog took all his food ; nevertheless, the output of nitrogen in the urine exceeded the intake. At this stage the output was much increased during the day on which the fever continued high, while on the days on which remissions occurred the increase of output was less marked. During the second fever period the average nitrogen output was the same as in the first period, but considerable daily variations occurred, the largest output being that of June 28 to 29, which amounted to 7·18 grammes, and was 2·49 grammes (= 44 per cent.) above the quantity ingested. During the third fever period the nitrogen output was higher than in the normal period, although the amount of food taken was diminished. In the final period the nitrogen deficit amounted on the first day to 7·175 grammes, and then diminished to about half this amount. The total loss of nitrogen during the whole experiment was 52·8 grammes. Assuming the amount of nitrogen in the animal at the beginning of the experiment to be 3 per cent. of its body-weight, the above quantity would represent 20·3 per cent. of the amount originally present. The body-weight changed during the experiment from 8·58 kilogrammes to 5·74 kilogrammes, a diminution of 39 per cent. The nitrogen in the fæces amounted during the first period to 24·4 per cent. of that contained in the food, during the second period to 19·75 per cent. of that in the food.

In addition to the above, the reader is referred to the older experiments of Naunyn, Senator, and Schimanski.

In man, since estimations of the urine before the onset of febrile states are not usually available, recourse must be had instead to determinations made during convalescence. During complete or nearly complete fasting careful note is required of the preceding dietary, the

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body-weight, the muscular condition, and the stage of inanition. Thus, on the third day of fasting, the nitrogen output is found to vary in different individuals between 7·9 and 15·1 grammes. A further comparison may be made if the patient is put upon the same diet as a healthy individual of the same weight and muscular condition. Observations can also be made during the transient elevation of temperature produced in man when tuberculin is administered.

Three (hitherto unpublished) examples of such determinations will now be given.

1. Male, aged twenty-six, weighing 63 kilogrammes, in fair muscular condition, without excess of subcutaneous fat, suffering from facial erysipelas. Nothing definite ascertainable (especially in reference to protein) respecting his preceding dietary. From the third to the ninth day of his illness patient received daily two cups (about 600 c.c.) of milk or weak coffee, some thin soup, 70 grammes of bread, together with water.

	Temperature.	*Nitrogen in Urine.*
		Gm.
4th day of illness ..	39·5° C. to 40·3° C.	22·4
5th ,, ,, ..	39·2° C. ,, 40·0° C.	17·7
6th ,, ,, ..	38·1° C. ,, 38·6° C.	18·2
7th ,, ,, ..	37·0° C. ,, 38·7° C.	17·1
8th day ..	36·7° C ,, 37·1° C.	8·4
9th ,, ..	36·5° C. ,, 36·8° C.	7·4

2. Female, aged twenty, strong, with little subcutaneous fat, weighing 55 kilogrammes, suffering from scarlatina (no kidney complication). Several days previously had taken little food. While under observation the patient received each day soup, one to one and a half cups (200 c.c.) of milk or thin coffee, 100 to 200 c.c. of white wine, occasionally less than 30 grammes bread, together with water. During the last few days patient received daily one to two additional cups of milk.

	Temperature.	*Nitrogen in Urine.*
		Gm.
2nd (?) day of illness ..	39·0° C. to 40·4° C.	18·3
3rd day of illness ..	39·6° C. ,, 40·2° C.	19·4
4th ,, ,, ..	39·3° C. ,, 40·2° C.	17·9
5th ,, ,, ..	39·2° C. ,, 39·8° C.	14·6
6th ,, ,, ..	38·8° C. ,, 39·6° C.	13·8
7th ,, ,, ..	37·6° C. ,, 38·8° C.	12·9
8th ,, ,, ..	37·8° C. ,, 37·9° C.	9·8
9th day ..	37·2° C. ,, 36·6° C.	8·7
10th ,, ..	36·4° C. ,, 36·5° C.	6·5
11th ,, ..	36·2° C. ,, 36·4° C.	7·2

3. Male, aged twenty-five, suffering from phthisis. Weight, 58 kilogrammes; muscular condition poor; marked emaciation. On two days, during which his temperature was elevated, the output of nitrogen in the urine was 14·3 grammes and 14·9 grammes respectively, while the intake was calculated to be 15 grammes. Tuberculin was then administered, the diet remaining unchanged. The output (third day, temperature 39·2° C.) then increased to 22·4 grammes, and on the following day, when the temperature fell, was 16·2 grammes.

In addition to numerous observations by older investigators, in

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particular Huppert and Riesell, many valuable contributions have been recently made, and are referred to by Müller in the first edition of this work. Making due allowance for omissions and sources of error, it is quite obvious from analysis of the urine that in man the output of nitrogen during an infective process exceeds the actual requirements of the organism. Infective conditions are, therefore, to be included in that group of pathological processes, described by Müller and Klemperer, in which an increased destruction takes place of body-protein, the store of which is thereby prejudicially affected. Biological considerations, however, teach us to be cautious in attempting to estimate the exact degree of protein destruction from the results of analysis. The protein metabolism is not affected in the same way in all infective processes, and is, in addition, influenced by the severity of the illness. According to our own experience and the results of published experiments, the nitrogen output during starvation usually exceeds the intake by a small amount—that is to say, by a few grammes. As will be seen later on, an exception is sometimes furnished by the terminal stage of infective processes ending by crisis. A relatively inconsiderable increase of nitrogen output is met with during the decline of subacute or chronic infective processes (septic infection, typhoid, tuberculosis). During the height of febrile conditions the protein destruction is considerably greater, often reaching an amount which is rarely attained by healthy people even on the richest diet. This is especially the case when individuals who are well nourished and of good muscular development, but not abnormally fat, suffer from high fever. Here, in reference to the view held by von Noorden, that an output of nitrogen amounting to 18 to 22 grammes per day is exceedingly high for healthy individuals on restricted diet, it may be observed that, nevertheless, perfectly healthy people occasionally eliminate during fasting 16 grammes to 23 grammes nitrogen daily in the urine. It is, however, not unusual for the output to exceed the intake (for example, in pneumonia) by nearly 17 grammes, representing 500 grammes muscle flesh. An average daily increase of output by 11 grammes nitrogen has been observed during an eight-day period in typhoid fever. In a case of caseating pneumonia, the patient lost in eight days 222 grammes nitrogen, representing 6,550 grammes muscle flesh. In no case, however, does the danger lie essentially in the extent of protein destruction, nor, for that matter, in the height to which the temperature rises. Respecting the connection between nitrogen output and the rest of the symptoms of fever, particularly body temperature, the nearly identical course of the two conditions at first attracted much attention. Considerable importance was attached to the old analyses of Jochmann and Traube, Moos, Redtenbacher, Uhle and others, which showed an increased output of urea in malaria when the temperature was high. It was shown also that a parallelism between the amount of nitrogen in the urine and the body temperature was met with in typhoid [Huppert, Brattler, Wingl, Wachsmuth, Warneke and others]; in acute rheumatism [Brattler, Wachsmuth, Huppert], notwithstanding the irregularity of the course of the fever; in exanthemata [Bartels, Brattler, Uhle]; and in septicæmia [Müller]. From

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this parallel the conclusion was formerly drawn that the elevation of temperature was brought about by precisely the same cause as the increase of urea. At the present time, however, such a conclusion would no longer be considered admissible, even if the increased nitrogen output were really parallel in its course to the rest of the symptoms of fever. In point of fact, it has now been conclusively shown, from a large number of observations, that such parallelism does not exist. All investigators are, at the present time, better acquainted with the really astonishing irregularity of nitrogenous metabolism exhibited during the decline of febrile processes, though the restricted diet taken remains very nearly constant—an irregularity which certainly stands in no recognisable relation to the variation of temperature and the intensity of the general symptoms. Such variations of nitrogenous metabolism are scarcely ever met with by healthy individuals on a constant diet, as are to be found in pathological states, such as Graves' disease. As an illustration of this point the following example, among others, was given by von Noorden in the first edition of this work :

A child, aged twelve, suffering from scarlatina, and receiving daily 1 litre of milk, two biscuits, and a small amount of soup and wine, representing in all 6·5 grammes nitrogen, eliminated in four days (temperature 38·7° C. to 40·1° C.) 9·2, 7·1, 10·4, and 7·8 grammes nitrogen respectively. In the presence of such differences, amounting to several grammes, the amount eliminated during a single day cannot be accepted as representing the average degree of destruction of protein. Again, not infrequently the elevation of the temperature is disproportionately shortened, and, nevertheless, the elimination of nitrogen is considerably increased—for example, in septicæmia, and also in typhoid fever. Sidney Ringer and Senator have shown that, when the rise of temperature in malaria is cut short by quinine, the increased destruction of protein runs a quite typical course. On the other hand, Pipping repeatedly failed to find evidence of increased destruction of protein in a young child suffering from scarlatina ; perhaps the rapid growth of the child would act as a compensating factor. The observations of the writer, like those of numerous other investigators, show that, with a medium diet, nitrogenous equilibrium is easily reached and maintained in phthisical individuals, who suffer from fever of an intermittent type. Futhermore, the increased output of nitrogen may become recognisable before a rise of temperature occurs (in malaria, for instance), and may diminish during the hot stage, rapidly disappearing in the sweating stage [Traube, Jochmann, Uhle, Redtenbacher, Sidney Ringer, Naunyn]. Here it may be remarked that May, and also Stähelin, were unable to discover any such pre-febrile increase in experimentally-produced infective processes. In tuberculous patients, Ringer observed that the amount of nitrogen in the urine diminished during the shivering stage, rose during the hot stage, and again rapidly sank during the sweating stage. A perfectly regular diminution of nitrogen output in the later stages of an acute infective process is by no means always the rule. A striking exception is met with in the relation which nitrogenous metabolism exhibits to the general condition of the patient, and also to the temperature, in the well-known epicritical

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elimination of urea. In cases in which the elimination of nitrogen during the elevation of temperature has been marked, as also in those cases in which it has been inconsiderable, there occurs at the time of, or subsequently to, the critical fall of temperature a very marked output of urinary nitrogen. Přibram and Robitschek, for example, record a case of relapsing fever in which, on the second day after the crisis, 107 grammes urea was eliminated, and in forty-eight hours 168 grammes. Naunyn similarly records a case of typhus in which on the day following the crisis 91 grammes urea was eliminated, and also a second case in which, during the third and fourth days following the crisis, 160 grammes urea was excreted. Additional illustrations are also afforded by von Noorden's observations on fever produced by tuberculin. A discussion upon pneumonia, in which, during resolution, a large amount of protein contained in the exudate enters the circulation, cannot, however, be entered upon here. In the extremely marked epicritical increase of urea accompanying the remission or cessation of fever there is exhibited a destruction of protein such as is otherwise reached only exceptionally during considerably increased ingestion of protein, but not, however, even in slighter degree, during the most powerful muscular exertion. Přibram and Robitschek, and subsequently Fürbringer and Zuelzer, observed that the elimination of sulphur runs, to a certain extent, parallel to this variability in the output of nitrogen. Salkowski further showed that the increased output of nitrogen is attended with an increased discharge of potassium salts. Further reference will be made later on to this paroxysmal epicritical elimination of nitrogen.

Krehl and Matthes have also shown that more protein is destroyed in the so-called aseptic fever than is the case in the normal organism under similar conditions, dietetic and physical.

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Considerable variations in the distribution of the nitrogen in the urine in different febrile conditions have not, so far, been encountered. Urea represents, on the average, 82 per cent. of the total nitrogen in the urine. The greatest pathological interest attaches to the increased output of ammonia, which takes place at the expense of the urea [Duchek,

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Koppe, Hallervorden, Leube, Bohland, Gumlich, and others]. Hallervorden observed in numerous infective diseases a not inconsiderable increase of the daily output of ammonia, reaching in pneumonia 2 grammes to 6 grammes, and in pleurisy and relapsing fever 2 grammes, as against about 0·7 gramme normally. The possibility of a connection existing between this increase of pneumonia and an excessive production of certain acids will be discussed later. During convalescence the amount of NH_3 present in the urine diminishes rapidly, and may even become subnormal.

Creatinin has almost always been found in increased amount in the urine in febrile conditions [K. B. Hofmann, Munk, Schottin, Moritz].

J. B. Leathes found that in hospital patients during fever the ratio of $\frac{\text{creatinin nitrogen}}{\text{total nitrogen}}$ was low—2 to 4·5, instead of 5 to 7. The subject of his further experiments was placed on a creatinin-free diet, and a febrile attack induced by injection of antityphoid vaccine, and the urine collected at intervals of three hours. As the temperature rose to 102·7° F. (rectum) the total nitrogen and crèatinin output increased, the curves coinciding exactly in time and shape. The rate of the creatinin excretion was increased about 25 per cent., that of the total nitrogen more than about 100 per cent. So that, in spite of the increased rate of creatinin excretion, the ration $\frac{\text{creatinin nitrogen}}{\text{total nitrogen}}$ fell to 3·2, instead of 5, its level during the preceding days. These results do not permit the application of Folin's view that the endogenous metabolism may be measured by the creatinin output in fever. The total nitrogen excretion in fever is increased much more than is that of creatinin.

Cario determined the daily output of uric acid (and also urea, chlorine, phosphorus, and sulphur) in a number of cases attended with febrile disturbance, and claims to have established that an increase of uric acid as a rule takes place. The same author, however, mentions a retention of uric acid occurring during febrile conditions, and investigates the influence of diuresis. According to Linser and Schmid the purin bodies, ammonia and amino-acids (determined according to Krüger and Schmid's method), are increased in pyrexia experimentally induced. On these and other points further investigation is required. It is not, however, surprising that a markedly increased elimination of uric acid should occur during resolution of an exudate rich in leucocytes, as in pneumonia.

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The causes or conditions of increased protein metabolism are certainly manifold, and up to the present have not been sufficiently elucidated.

In the first place, the part played by the rise of temperature in itself must be examined. The increased production of heat is not simply dependent upon metabolism ; the latter is also conditioned by the former. As a matter of fact, in most of the experiments in which pyrexia has been produced by the application of heat externally, an increased output of nitrogen has been noted. Recently Voit has conclusively proved that in fasting animals such pyrexia is attended with an increased nitrogenous metabolism ; well-fed animals exhibit, moreover, a considerably smaller degree of protein destruction. It is surprising that very variable individual results were obtained in all the older experiments on the action of pyrexia upon protein disintegration. Only Koch and Simanowski failed to observe an increased cleavage of protein. These two authors, employing animals which had been carefully brought into metabolic equilibrium, observed that in pyrexia produced by warm water or heated air there was an actual diminution of nitrogen output, and Simanowski regarded this absence of increased protein destruction as constituting an important distinction between simple pyrexia and pyrexia due to an infective process. Richter pointed out that these results were probably due to the application of external heat being of too short duration, and, further, that the increased breaking down of protein may easily be overlooked, since it often does not follow immediately upon the heating. In pyrexia due to puncture of the corpus callosum, Aronsohn and Sachs likewise found an increased destruction of protein, the difference from the normal being by no means inconsiderable. Girard obtained the same result. Schultze, working under Krehl's direction, showed that the nitrogen output by animals which had been trephined was, nevertheless, somewhat small (20 to 30 per cent.), and, in any case, was not to be compared with that in infective fevers. The attempt made by Schultze, and afterwards by Rolly, to establish on this account a fundamental difference between metabolism after puncture and that occurring in infective processes, will be considered later. It may, however, be pointed out that recently Senator and Richter, repeating these experiments, again attribute a very marked increase of nitrogenous metabolism (20 to 30 per cent.) to the influence of simple pyrexia. When one considers that rabbits, upon which alone these observations have been made, are not very suitable animals for such experiments, it may well be inferred that successful puncture would lead to only a medium increase of nitrogen output. Perhaps, also, the animals experimented upon exhibited individual variations. We regard it as by no means established that the protein destruction following puncture is exclusively related to the simple pyrexia thus induced.

Schleich and Topp found that, when in man the body temperature was raised by preventing loss by radiation, a similar increased nitrogen output followed. Recently, Linser and Schmid have shown that a rise of body temperature in man, caused by external application of heat, and continued intermittently for several days, is not attended with an increased breaking down of protein, so long as the temperature does

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not rise much above 39° C., but that such increase appears when the body temperature reaches or exceeds 40° C. When carbohydrates are administered in experimentally induced pyrexia, the nitrogenous metabolism is not limited to the same amount as when the temperature is normal; an increased protein destruction takes place in pyrexia in the presence of carbohydrates. Krehl's conclusion, that in infective fevers under 40° C. the additional protein cleavage is caused exclusively by the infection, is therefore justified. It is equally certain that when the body temperature is at its highest only a very limited portion of the nitrogen excreted can be directly attributed to the pyrexia. Although Senator and Richter, partly influenced by the earlier conclusions of Richter, in their critique on Hirsch and Rolly's observations and theories (again discussed later on), assert that in pyrexia, no matter how caused (by puncture, external application of heat, or bacterial infection), the nitrogen output increase is due to the raised body temperature, it would, nevertheless, appear that this assertion is in reality aimed at those who seek for the cause of the raised body temperature solely in the abnormally increased protein destruction. In infective fevers, however, the whole of the increase of nitrogenous metabolism cannot, even in the light of Senator and Richter's most recent work, be regarded as conditioned solely by the raised temperature. Undoubtedly, a very appreciable fraction must be attributed to the exciting cause of fever.

This larger fraction of febrile protein disintegration, not occasioned by the rise of temperature, is not to be accounted for merely by the breaking up of inflammatory exudate. Of course the protein contained in the latter represents food protein or body protein, temporarily withdrawn from, but afterwards to be returned, during resolution, to the body juices, causing then an increased production of urea. F. Müller rightly conjectures that in inflammatory tissue a specially active destruction of protein takes place in consequence of the continual advent and destruction of cells. The increased cleavage is, however, just as great in those infective processes in which no exudation worth mentioning occurs, and is observable not merely during or after the absorption of such exudates, but also during their development (in pneumonia, for instance), so that more effective factors than mere absorption of an exudate must come into play.

Furthermore, the condition of inanition of patients suffering from fever must be borne in mind. It has been believed that the increased nitrogenous metabolism in fever could be divided into a compensatory and a non-compensatory portion. By means of an abundance of rich nourishment the increased protein destruction can be considerably diminished, though it is difficult to abolish it. The compensatory cleavage would correspond in fever to the accompanying inanition, while the non-compensatory portion would be conditioned by the cause of the fever. This being so, it would follow that the amount of nitrogen in febrile urine is principally determined by the kind of food taken—a conclusion which is not very probable *a priori*. Hirschfeld was of opinion that the protein destruction of patients suffering from fever could by a suitable dietary be made equal to that of healthy people on the same

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diet. His attempt to establish this proposition was, however, unsuccessful. Weber next observed that a sheep which he had under observation lost protein during an acute febrile state (produced by injecting a watery extract of glanders bacilli, this causing pyrexia, without, however, leading to complete refusal of food), although it took an amount of nourishment which would, under normal conditions, maintain nitrogen equilibrium and yield a sufficient amount of available energy. When the protein exchange of the animal was considerably raised, and pyrexia then induced, at the same time an abundance of protein and carbohydrate being administered, the protein exchange was maintained unchanged during the whole of the fever period. In the same way, Weber succeeded in bringing the animal after a period of fasting into a nitrogenous equilibrium during pyrexia by administering a sufficiently rich diet. Nevertheless, since the normal amount of nourishment is not easily administered during fever, Weber was not able to ascertain with certainty if the diminution of protein metabolism attainable by means of carbohydrates was sufficiently marked to lead to equality with the febrile protein metabolism ; no sufficiently accurate determination of the extent to which the administration of sugar exercises a protective action is by this means possible. More important than the fact that the nitrogen metabolism in fever cannot be accurately altered to the normal is the obvious impossibility, revealed by these experiments, of demonstrating quantitatively, by this mode of investigation, the existence, in addition to the ordinary protein destruction, of an additional cleavage attributable to the excitant of fever.

To this latter the ill-defined term " toxic " destruction of protein applies. It is preferable, however, to define the " ordinary " destruction of protein as including the whole of the protein destruction taking place within the living cell, no matter whether this is conditioned by the kind of diet taken or is dependent upon toxines. We are already acquainted with two fundamentally different modes of liberating energy in the organism—namely, the direct setting free of energy by the cell, and the production of heat by other thermo-chemical processes independently of the cells—such, for example, as fermentation. In pathological processes in particular there is met with, in addition to the natural processes by which energy is liberated, a further process, autolysis, in which protein destruction occurs outside living cells, conditioned by the setting free, through auto-digestion, of certain ferments in necrotic tissue. This form of protein destruction is in some respects comparable to that occurring, for example, in phosphorus-poisoning, in which the liver cells are severely injured ; so that the assumption of a process compensating for the fermentative destruction of protein taking place in the body juices, by substitution of carbohydrates, encounters difficulties. The metabolism taking place in living cells is, in fact, itself conditioned, on the one hand, by the affinity of the cell substance for individual food-stuffs, in particular for protein, and, on the other hand, by the composition of the fluid forming the medium of the cells of the organism. The cell prefers that substance which is offered to it in greatest abundance, and this is the reason why carbohydrate is chiefly

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used up, and, in consequence, protein destruction reduced to a minimum, when protein is administered in small and carbohydrate in large amount. For the maintenance of life the cells require to be supplied with food molecules capable of furnishing energy. We cannot form even an approximate idea of the extent to which, in addition to normal energy production, heat is produced by simple fermentative processes. At any rate, neither fatty degeneration of muscle nor cloudy swelling of glandular organs stand in direct relation to the increased breaking down of protein met with during the decline of febrile processes.

According to the earlier conception, the mode of action of toxines depended upon the common property of these substances of entering into combination with living cells through the agency of specific haptophore groups present in the body fluids. While desiring to avoid repetition, it may be again pointed out that Ehrlich's side-chain theory explains both the defensive function of the body and its assimilation and breaking up of food-stuffs in the same manner. Toxines possess haptophore groups, just as do food-stuffs, and the mechanism of their attachment is the same. In accordance with the mode in which, for example, protein immunity is portrayed in protein metabolism, it was inferred that the immunized organism had acquired an increased capacity for digesting foreign protein, the whole of the increase of nitrogenous metabolism constituting, so to speak, the price paid for this increased capacity. Apart from the severance from the cell of the groups forming the antibody, a toxic action of the attached foreign protein comes into play at the same time. Why should not a destruction of protein occurring in the living cells of the peculiar character above described be in the main compensated for by carbohydrate, just as is ordinary protein destruction? We believe that, for the explanation of the increased destruction of protein in the course of infective processes, we must turn to the processes taking part in the production of immunity. In support of this view we may refer the reader to p. 94, and also call attention to the irregularity of the nitrogen elimination, and in particular to the epicritical elimination of urea, with its accompanying change in the general condition, so frequently observed in clinical practice. This epicritical elimination has been attributed to disturbed kidney function, to accumulation of urea in the body fluids and tissues due to delayed excretion, to injury to cell-protoplasm followed by liquefaction and elimination of the necrotic cell substance, and to the formation of certain complicated nitrogenous substances, which are at first retained and are not decomposed with formation of urea until the fever begins to subside. All these explanations are either inadequate, or lead in the direction just indicated. When it is admitted that irregularity in the output of urea occurs, the important point is that urea is formed. The rapid rise of nitrogen elimination in the goat immunized against egg-albumin offers many points of comparison with epicritical elimination of urea.

In attempting to determine the factors concerned in bringing about the increased protein metabolism of fever, the mistake has been made of discussing the increased nitrogen elimination without reference to the remaining metabolism and to the total energy required, and also of assum-

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ing that here, as elsewhere, protein destruction is to a certain degree governed by special laws, or, at any rate, of making the loss of nitrogen the central point. At the present time nothing positive can be asserted respecting the dynamical aspect of protein destruction in fever, though a study of the matter from this point of view is certainly a step in the right direction.

In our present conception of febrile metabolism most attention is directed to protein metabolism. Until lately no accurate information respecting the associated combustion of fat in febrile conditions was available. It was thought that the latter was of the type accompanying insufficient supply of food. In Section 4 we shall see that in fever the production of heat is increased. This increase of heat proceeds exclusively from chemical change, as does the heat-production of healthy individuals, this being also the only source available in febrile conditions. The existence of special heat-producing processes in fever, which theoretical considerations led Herz to assert, must be absolutely denied, since a complete agreement is found between the caloric values, whether determined directly or indirectly (by chemical methods), as has been insisted upon by Krehl and Matthes in numerous and widely varied experiments. Of the two alternatives, that in infective processes oxidation undergoes a general increase, the oxidation of fat being included therein, or that the increased heat-production is due to protein destruction alone, the latter is the more generally received. It is still unsettled how far different infective processes resemble each other in this connection. For one febrile disease (see p. 125), however, in which very rapid loss of strength occurs, it has been conclusively shown by Stähelin that increased protein disintegration is accompanied by directly increased destruction of fat.

A general settlement of this problem can only be arrived at after prolonged experiments, in which both metabolism and heat-production are fully investigated. If the increased metabolism is chiefly of protein, the calories derived from protein destruction will account for most of the increased heat-production. If the increased production of heat is an effect of chemical heat regulation, it will be exhibited as brought about by increased combustion of fat. The absolute amount of nitrogenous metabolism is, of course, also altered in a manner comparable to that of the fat. Similarly, the nitrogen equilibrium will be affected, perhaps, in a manner comparable to that observed by Weber in a sheep during pyrexia.

The problem is now changed, in that fresh experiments are required to ascertain if the former of the above two cases is the more frequently realized. Stähelin's dog affords a fair example of the second case. The proteins, indeed, take in this experiment a somewhat larger share than in the preliminary period in the total production of heat, but nitrogenous metabolism is, nevertheless, as has already been indicated, a very complex function, intimately related to fat storage, inanition, and heat-production, and in this experiment the actual increase was first observed when the temperature commenced to fall.

In Section 6 we shall attempt to show that the essential feature of febrile rise of temperature is that the nearly normal functioning of

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the heat-regulating centre is adjusted to a higher level than usual. This alteration of heat-production to a raised scale means that the regulative centre is so stimulated, or its sensitiveness to stimulation is so affected by the cause of the fever, that it now reacts to the external temperature as if this afforded a stimulus to heat-production by being very slow. Proceeding from this standpoint, the co-ordinated change of general metabolism usually present in infective processes may easily be referred to a disturbance in the same direction.

Rubner's theory of the consumption of energy naturally has special reference to hunger, temperature of the air, and certain physiological needs. It is, however, quite immaterial whether the demand for an increased consumption arises from actual cold in the external world or from a bodily state in which the organism responds more strongly to external loss of heat. For the normal range of external temperature there must exist in such a state of the body a definite increase of heat production, which the organism strives to obtain by chemical heat regulation. The minimal supply of heat is increased in consequence of the increased sensitiveness of the thermotaxic mechanism, the katabolism of the body being raised. Stimulation does not invariably cause continued overaction, fatigue sometimes ensuing, as is observed in other mechanisms subjected to stimulation. This is seen in the phases of febrile infection in which oxidative processes are not persistently high.

The case first considered, in which albumin brought about the consumption of stored-up fat, cannot, moreover, be neglected when investigating the supply of energy. The increased nitrogen metabolism may equally have a similar significance in respect of heat-production. Rubner, as is well known, attributes a special thermal significance to the breaking up of the protein molecule into a nitrogenous and a non-nitrogenous fraction; it is principally this breaking up, representing, as it does, a special dynamic effect, which results in excessive heat-production. The bodily condition, which, as above described, results from the stimulation caused by the exciting cause of the fever, furnishes a plausible explanation of this separation of the nitrogen-free fraction. Even normally, the circulating fluid excites an increased consumption in certain organs, though not in all the cells of the body. In fever it may be that, in consequence of stimulation due to organic combination with toxins, the cells of glandular organs are most affected, and that in these the breaking up of protein mostly occurs. The nitrogenous fraction, as we have seen, is rapidly oxidized, and appears in the urine; while the non-nitrogenous fraction, which Rubner regards as including carbohydrate groups, is more slowly oxidized, because an increased heat production in certain organs is attended with a lessened production elsewhere. In this respect the organism during fever is comparable with a normal organism, into which an abundant supply of albumin has been introduced.

Of course it must be admitted that the foregoing conjectures are merely advanced tentatively as a provisional explanation. They may, however, be accepted with confidence as throwing some light upon the dynamic relations of febrile protein destruction. In the second case,

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calories derived from protein replace calories derived from fat; in the first case, however, they represent increased heat-production, and the destruction of protein cannot be checked by carbohydrates.

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The manner in which protein is broken up in febrile conditions has often been imagined to be quite different from that occurring normally or during fasting. The occurrence in fever of qualitative alterations of the mode of protein destruction is not yet established. Significance has, however, been attributed in this connection to various experimental results.

In the first place, anomalous carbon elimination in fever has been referred to altered protein destruction. Thus, certain unexplained changes in the respiratory quotient $\frac{CO_2}{O}$ have been regarded as indicating modified oxidative processes (see p. 129). Again, a similar significance has been attributed to the increased carbon elimination in the urine of rabbits, first noticed by Loewy, and subsequently by May, who regarded it as characteristic of febrile urine. The ratio C : N, which became markedly higher when the animals experimented upon were fasting, diminished during fever; compounds thus appear in the urine which are poorer in nitrogen and richer in carbon (especial prominence being given to creatinin by May). In the dog, however, Stähelin found that the above ratio varied, as in the normal animal, between 0·732 and 0·758. In human beings, the subjects of fever, Scholtz, working in our laboratory, was unable to detect any constant relative increase of carbon output; in pyrexia due to the injection of tuberculin, he found increased elimination of carbon, but no abnormal change, in pneumonia and faucial angina; while in typhoid fever the output was diminished. Mohr, continuing these investigations, also found that the relative carbon elimination was sometimes higher when the temperature was raised; nevertheless, such variations were not supernormal, so that no pathological significance could be attributed to the carbon output on the ground of such variations of the $\frac{C}{N}$ quotient. Furthermore, in some of the experiments the pyrexial elimination of carbon was less than the apyrexial. Altogether opposed to the assumption that an increased elimination of carbon occurs in febrile states are those experiments in which, during severe remitting fever, the value of carbon and the ratio C : N are quite unaltered.

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In order to be in a position to criticise the above results, the relation and the significance of carbon in normal urine must be considered. The circumstance recorded by Voit, Rubner, and others for animals, that the output of carbon in the urine is normally greater than corresponds to the urea eliminated—in other words, is greater than 0·43—is true also for man [Scholz, Bouchard, Pregl]. Scholz, in a large number of analyses of healthy human urine, found that the ratio C : N ranged between 0·72 and 0·93. Van Oordt obtained the figures 0·99 to 1·32 for the urine of infants during suckling. Bouchard, who regarded the extent of the ratio C : N as affording an indication of the toxicity of the urine, obtained a mean of 0·87 from observations carried out on seventeen different individuals. The kind and amount of food given appears, according to Rubner's experiments on the dog, to influence the amount of the C : N ratio of the urine; with albumin as food this ratio became 0·532, on a flesh diet 0·610, and during hunger 0·728. It has been pointed out by Pregl, Dongé, and Lambling that even when all the organic substances now known to be present in the urine are taken into account, the above figures are not reached; a considerable excess of carbon remains. This circumstance explains why the assumption is made that, normally, substances are eliminated in the urine which possess a relatively small amount of nitrogen as against carbon, or consist of nitrogen-free carbon compounds. Such are the carbohydrate substances to which Landwehr, Baumann, Baisch, and others have called attention, and which have recently been studied in pathological conditions by Rosin and Alfthan. These are normally eliminated in such small quantity that they cannot appreciably influence the amount of carbon in the urine. On the other hand, the substance termed oxyproteic acid by Bondzynsky and Gottlieb, and called uroproteic acid by Cloetta, claims notice both on account of its composition and of its amount in the urine. The ultimate analyses made of this substance, which do not, indeed, agree very closely, exhibit a considerable amount of carbon and a relatively small amount of nitrogen. Opinions are also divided as to the quantity of this substance excreted, but figures of 3 to 4 grammes daily indicate that it almost equals the urea output. The amount eliminated appears, however, to be inconstant, as would be expected from the variations exhibited by the C : N ratio.

According to Krehl and Matthes, protein destruction takes, in fever, a course which is qualitatively abnormal, in that breaking down is effected by hydration. In this connection Krehl referred to the abundant appearance of albumoses (chiefly deutero-albumoses) in the urine of animals and of men in febrile conditions. Schultess, who gives a summary of Krehl's investigations, finds, on precipitating with alcohol and using the tannin test as a control, that in non-febrile illnesses albumosuria cannot usually be detected, while in febrile affections marked albumosuria often occurs. This is, according to Schultess, the case in scarlatina, diphtheria, influenza, and typhoid, the albumosuria corresponding in degree to the rise of temperature, and disappearing when the latter becomes normal. If albumosuria makes its appearance, it is found that when the albumin is removed albumose can be demon-

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strated. Krehl, Matthes, and Schultess have never failed to discover albumose in febrile urine.

Since the amount of so-called " peptonuria " varies widely in different infective processes, such as pneumonia and typhoid, and appears to be quite explicable by Maixner's hypothesis that the peptone of the urine (deutero-albumose) is derived from broken-down leucocytes, we were led, with Jewett, some years ago, to undertake a series of observations upon patients suffering from these two illnesses in which albumoses were found always present in the blood. Both Hofmeister's method and that of Devoto were employed, and the result regarded as positive only when both were successful. The amount of blood examined was almost always 100 c.c., and the results were as accurate as was possible at the time. We were surprised to find that in typhoid—in which the average amount of albumosuria is relatively small—more albumose is present in the blood than in pneumonia. Speculations arising out of Krehl's conception of the etiology of fever had originated these observations. We deferred publication because in control experiments calves' blood (this blood was defibrinated, came directly from the slaughter-house, but nothing was known respecting the feeding, etc., of the animals, which were presumably healthy) was found occasionally to contain recognisable amounts of albumose.

Krehl, who has been led by his recent experiments to relinquish his original view, that albumoses constitute pyrogenous material *κατ' ἐξοχήν*, now, on the contrary, regards as plausible the assumption that the disturbance of heat regulation is brought about by the products resulting from the hydrolysis of protein. Hirsch follows him in this. According to this theory all the numerous pyrogenous substances would lead to an increased destruction of albumin, and if this proceeded along definite lines substances disturbing the production of heat would be formed, and fever result. If, however, the presence of albumose in the blood and urine is to be taken as an indication of abnormal destruction, hydrolytic or other, of protein, then this conclusion would appear somewhat dubious. Moreover, the fundamental biochemical data necessary to enable a decision as to the occurrence of a qualitative alteration of protein destruction in the organism are wanting. In the first place, albumosuria is not exclusively related to fever. Still more important is the fact that albumoses in all probability form a normal constituent of the blood [Embden and Knoop, Langstein, Joachim, von Bergmann and Langstein]. Abderhalden and Oppenheimer have, indeed, obtained opposite results; perhaps, however, they have worked with too small amounts of plasma or serum. It is more natural to attribute febrile albumosuria to altered circulatory and eliminative conditions (*e.g.*, altered permeability of the kidneys) than to regard their appearance as an indication of a qualitative change in protein destruction, the more so since the amount of albumose in the blood does not run parallel to the degree of albumosuria present. Finally, it may be observed that such physiological and pathological conditions as cystinuria and alkaptonuria indicate that protein destruction in the cells of the healthy organism is at first hydrolytic. But little that is certain is, however, known in this connection.

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3. Physical and Chemical Changes in the Blood and Blood-forming Tissues in the Course of Infective Processes and of Immunization.

Variations in the physical constants of the blood and serum (specific gravity, freezing-point, electrical conductivity, refractive index) are inconstant and inconsiderable. These will, therefore, not be considered in detail.

The changes in the total protein content of the blood, and in the relative proportions of albumin and globulin in infected and immune animals, have been more fully investigated, and are more characteristic.

Szontagh and Wellmann found an increased amount of protein in diphtheria serum, which they thought was possibly related to the altered feeding of the immunized animals. Butjagin observed a similar increase, and pointed out that it closely followed, and was therefore dependent upon the accumulation of antitoxin in the blood. Although Joachim and Moll found the protein content raised only to an inconsiderable degree in immunization to diphtheria toxin, and to various natural and chemically changed proteins, yet to these experiments the objection of Langstein and Mayer applies—namely, that the investigation of serum protein alone can only afford a partly correct idea of the variation of the protein content of the blood during the course of infective processes. According to Langstein, the plasma must be investigated. In it the protein content is raised during the course of very many immunization processes. Langstein and Mayer first experimented with the plasma of rabbits infected or immunized with typhoid bacilli, dysentery bacilli, pneumococci, streptococci, bacilli of swine erysipelas, and with cholera vibrios. The total protein of the plasma of normal rabbits amounts to 0·4775 gramme in 12 c.c.; after infection with typhoid bacilli this was found to be 0·5399 gramme, with pneumococci 0·5226 gramme, with streptococci 0·5395 gramme, etc. M. Mayer found, however, that in the dog the blood plasma, which normally shows marked variations in total protein content, exhibited no notable increase after infection with nagana (tsetse-fly disease).

The relation of globulin to albumin under the same conditions as to infection and immunization is quantitatively greater, and appears to possess a higher significance. Joachim observed that the globulin of horse serum underwent a considerable increase, relatively to the

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albumin, during the process of immunization to diphtheria toxin. Moll showed that this increase of globulin was a phenomenon constantly met with when rabbits were immunized with foreign protein (horse serum, albumin), but he wrongly assumed that the total protein content of the blood remained unaltered. These observations were confirmed by an extended series of observations upon infective processes made by Langstein and Mayer, who found that in normal rabbits the ratio of total globulin (fibrinogen plus serum globulin) to albumin varied between $\frac{1}{2}$ and $\frac{1}{3}$, and that in nearly all the infected and immunized animals the total globulin increased, so that the ratio became less than $\frac{1}{2}$, and even sank to 1 : 1. The ratio of serum globulin to albumin, normally between 1 : 2·3 and 1 : 3·6, does not usually fall much below $\frac{1}{2}$ in infected rabbits. In trypanosomiasis (nagana) of the dog the proteins of the blood are changed as in bacterial infection ; the blood-plasma exhibits an increase of total globulin and a considerable diminution of albumin, the ratio of the two (normally 1 : 1·5 to 1 : 1·9) sinking to less than 1 : 1. A direct causal connection with the formation of antibody cannot be regarded as established, although the antitoxin is present in the globulin fraction of the blood. As a matter of fact, however, it would appear that in this complementary relation of the principal proteins of the blood a fairly constant reaction of the blood to the toxic effects of bacteria obtains. It must be added that Glässner, who, by immunizing with bacteria, toxines, and proteins, likewise obtained an increase of globulin when the animals exhibited marked disturbance of nutrition, regarded this increase as a secondary result of the inanition attending immunization. Although, according to Githens, the amount of globulin in the blood increases in dogs during starvation, nevertheless Glässner's assertion that increase of globulin and immunization are in no way related is much too sweeping.

As regards the fibrin or fibrinogen content of the blood, Th. Pfeiffer distinguishes between two classes of infective diseases, in one of which (typhoid, malaria, septicæmia without metastatic abscesses, nephritis) the amount of fibrin is unaltered, while in the other (pneumonia, articular rheumatism, erysipelas, scarlatina, peritonitis) a marked increase takes place. This increase is, according to the older observers, most marked in fibrinous pneumonia. The second of the above groups is, as is well known, characterized by increase of leucocytes in the blood and by albumosuria. Langstein and Mayer supported Pfeiffer's clinical observations by showing that animals inoculated with pneumococci exhibited a marked increase of fibrinogen, while those inoculated with typhoid, cholera, dysentery, and swine erysipelas organisms showed little change from the normal. It must, therefore, be concluded that the power of increasing the fibrinogen of the blood is a special property of pneumococci and streptococci.

Müller then investigated whether changes similar to those in the blood-plasma took place in the tissues of infected and immunized animals. He selected in particular organs containing lymphoid tissue, because the observations of Pfeiffer and Marx, Wassermann and others, pointed to the spleen and bone-marrow as the probable place of origin of a series of

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defensive substances, and the researches of Wassermann indicated that the fate of the pneumococcus was decided in the bone-marrow. Müller, using the method devised by Hofmeister, Pohl, and Reye, instituted a comparison between blood-plasma and bone-marrow, in respect of fibrinogen, globulin, and albumin. Animals infected with typhoid showed in the bone-marrow extract a marked increase of total protein, as also a still more striking absolute increase of fibrinogen fraction, which was more than doubled, and exhibited a percentage increase as well. In the bone-marrow extract of staphylococcic animals a small increase of the fibrinogen fraction was found, together with a considerable increase of albumin. Contrasting the two, a certain parallelism between the changes in the blood-plasma and bone-marrow extract is observable. The fibrinogen fraction of the bone-marrow extract cannot be attributed to the blood-plasma it contains, but evidently has its origin in the lymphoid tissue itself. The simplest assumption is that an increased production takes place in the bone-marrow.

Müller's results are perhaps capable of throwing some light upon the ultimate source of fibrinogen. Up to the present a genetic relation of fibrin to the white blood-cells has been generally assumed. Pfeiffer has, however, recently shown that the above described coincidence of increase of leucocytes with that of fibrin only holds for infective leucocytosis, and is not met with in leuchæmia. The difference observable between Müller's observations on the fibrinogen of the blood-plasma of man in typhoid and those of Pfeiffer may be attributable to a difference in the distribution of the fibrinogen fraction between lymphoid tissue and plasma.

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4. Total Metabolism and Consumption of Energy in Febrile States.

At the present time the problems studied in the present section are investigated, on the one hand, by means of the respiration technique devised by Speck and Zuntz, more particularly the latter, and, on the other hand, by means of the procedure of Pettenkofer and Voit. A comparison of the relative values of the two methods would be out of place here. In reference to the well-known objections raised by Ebstein, Fick, Fritz Voit, and others against conclusions on general metabolism being drawn from experiments of short duration made with Zuntz's

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method, it may be pointed out that in reality the investigation of a whole series of physiological and pathological problems has been considerably advanced by the employment of this method. For individual problems one or the other method is perhaps preferable, but scarcely a single fact established by the one method has been appreciably modified by the use of the other method. Of course only gross general metabolism can be studied by Zuntz's method; furthermore, many important problems such as fat destruction in fever, can be investigated with accuracy by observations on respiration extending over the whole of the day, taking account of urine and fæces, and, in consequence, dealing with total metabolism and the intake and output of energy.

The problem of a possible increase of consumption of carbon during fever was naturally first suggested by the recognition of increased nitrogen metabolism during fever. Theoretical attempts to show that increased production of heat is responsible for the elevated body temperature in fever [Liebermeister, von Leyden] led to a more complete study of total metabolism, in particular of oxidative processes in pyrexia. For some time it was considered sufficient to estimate the carbon dioxide expired. Leaving, however, out of consideration minor circumstances, which may affect the excretion of carbon dioxide compared with the much more stable consumption of oxygen, it is obvious that the study of a single gas in the expired air can merely give information respecting quantitative changes. Any qualitative variations of the oxidative processes which may possibly occur are far more readily recognisable if, in addition to estimation of the CO_2 output, the consumption of oxygen is also ascertained, and the relation of the two $\left(\frac{CO_2}{O}\right)$ determined. The literature of the subject indicates the considerable progress which has been made in this direction. Senator, who repeatedly determined febrile metabolism by means of carefully devised experiments, combining examination of the constituents of the urine with that of respiratory changes, was the first to establish the absence of so marked an increase of carbon dioxide output as to lead to the conclusion that in every case of febrile illness more nitrogen-free material is destroyed than is the case when the temperature is normal. It was, indeed, Senator who advanced the proposition, constantly debated ever since, that in fever more protein and less fat is used up, the organism becoming in consequence poorer in protein and relatively richer in fat. Febrile fatty degeneration appeared at first to support this theory.

Following the numerous investigations of Silujanoff, von Leyden, von Leyden and Fraenkel, Colasanti, Reynard, Finkler and Lilienfeld, nearly a decade elapsed during which no further study of the respiratory changes in fever appeared. Under the influence of Liebermeister, and still more of Pflüger, the opinion again became firmly held that the rise of temperature in febrile conditions was the direct result of increased metabolism. At this time (1891) we again turned our attention to the subject, relatively little being known concerning several important details, particularly the absolute amount of O_2 taken up by the human subject, and also the respiratory coefficient in fever, though, according

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to the current teaching, the subject was regarded as fully worked out. We laid stress upon the necessity of controlling experiments on animals by means of observations made upon the human subject during fever, and we found that increased oxidation was not an essential accompaniment of fever, for, though often present, it did not occur to the extent which the older experiments, as also *a priori* considerations would have led us to expect. In addition, fever occurred more often than had been supposed to be the case without oxidative processes being increased to a recognisable extent. Furthermore, no direct relation was found between extent of oxidation and degree of pyrexia, so that we were forced to conclude that any qualitative alteration of febrile metabolism which might possibly occur was insufficient to influence the respiratory coefficient in a recognisable degree.

Since then Loewy, Speck, R. May, Riethus, Svenson, Robin and Binet, Stähelin, Kaufmann and others, have made valuable experimental and clinical observations which have increased and extended our knowledge, partly by Zuntz's method, partly by that of Pettenkofer and Voit. The part which combustion of fat plays in fever is, however, still under discussion. R. May and Hirsch lay particular stress upon the increased destruction of carbohydrates, especially of glycogen.

Two recent valuable experimental researches by May and Stähelin, already in part described, will now be further considered.

May's experiments were carried out on rabbits in which rise of temperature had been brought about by inoculation with the bacillus of swine erysipelas. The animals had been starved some days previously, in order that heat production and protein destruction might reach a stationary condition. The nitrogen output, O_2 consumption, and CO_2 production were determined. For the gaseous exchange a small Voit's respiration apparatus was employed; in this the animals remained, in each individual experiment, about twenty-four hours.

May's observations were carried out on normal rabbits as well as upon rabbits in which fever had been induced. The normal fasting rabbits passed at the end of two days into a condition in which a uniform nitrogen output corresponding to their nutritional state and weight was maintained. The CO_2 production sank markedly from day to day; it is well known that in man, on the contrary, the same rate is long maintained.

The increased nitrogen elimination in animals in which a rise of temperature has been induced begins on the second day of fever, and has been already discussed. Respecting the carbon elimination, great interest is attached to the relation observed by May to exist between nitrogen and carbon in the urine. During fasting this ratio increased in one case from 1 : 0·7851 to 1 : 0·708, to sink again during fever to 1 : 0·7911. This point has already been referred to.

The carbon elimination from nitrogenous material, running parallel to the nitrogen elimination, May found to be increased in febrile states. The carbon elimination from nitrogen-free material appeared to undergo no increase in febrile conditions.

The total calorie production, calculated from the protein metabolism,

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and the carbon output in the urine and in the expired air, was found, on the first day of fever, to be identical with that of the preceding normal days. This is not contrary to what occurs in the fed dog, though it differs from what is usually observed in man. On the second day, when the fever was fully developed, an increase of 5 per cent. to 28 per cent. was observed. On the third day of fever a reversion to the former condition was observed. The respiratory quotient became slightly less during fever. May attempted to investigate the rise of calorie production in two ways: by comparing the individual days of the experiment one with another, and, when this was impossible, by comparing the heat production of the febrile animal with that of a normal rabbit having the same weight. We subjoin the result which May obtained, using the first method:

	Calories—		
	Total.	Per Kg.	Per Square Metre.
Rabbit D:			
1st fever day	102	44	554
2nd „ „	127	58	584
Per cent.	+24·5	+31·8	+5·4
Rabbit E:			
1st fever day	152	64	660
2nd „ „	166	73	746
Per cent.	+9·2	+14·1	+12·9
Rabbit G:			
1st fever day	146	55	542
2nd „ „	154	61	646
Per cent.	+5·5	+11	+19·2

The reader can obtain the percentage distribution of the protein, fat, and carbohydrate destruction as far as calorie production is concerned, for one of May's experiments (rabbit E), from the table given on p. 124. Although in this, as in all the experiments, an increased protein cleavage occurs, it does not necessarily follow that the amount of fat destruction is in point of fact diminished. In one of May's experiments (rabbit D) the amount of carbon derived from nitrogen-free material increased on the first day of fever (the fourth day of fasting) by 0·788 grammes—that is, by 20 per cent. In the other cases no such marked increase occurred, the figures obtained showing slight decrease. Since, however, during fasting, the carbon output derived from nitrogen-free material continually diminishes, it follows that if this carbon output remains unchanged during fever, this must be considered to be equivalent to a slight increase. May was able to exhibit this relation most clearly by expressing the calorie value per kilogramme of body-weight.

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	Calories from—		Remarks.
	Nitrogen-holding Substances.	Nitrogen-free Substances.	
Rabbit E: 3rd day ..	18·0	44·0	—
„ „ : 4th „ ..	19·0	45·0	Commencement of fever.
„ „ 5th „ ..	27·0	46·0	Fever.
„ G: 3rd „ ..	16·8	37·0	—
„ „ 4th „ ..	18·5	35·6	—
„ „ 5th „ ..	20·6	34·8	Commencement of fever.
„ „ 6th „ ..	27·9	33·3	Fever.
„ „ 7th „ ..	27·2	41·9	—
„ H: 3rd „ ..	10·7	53·8	—
„ „ 4th „ ..	10·4	53·7	—
„ „ 5th „ ..	11·8	54·0	Commencement of fever.
„ D: 3rd „ ..	23·5	20·9	„ „
„ „ 4th „ ..	31·6	26·9	Fever.

It is seen that rabbit D shows, as already mentioned, a marked increase of fat destruction, while in the other animals there is a tendency, not, however, very striking, in the same direction.

May's work is replete with valuable data. Some of his conclusions, nevertheless, as is indicated in this section, are not to be accepted without reserve. The abstract of May's work, which is here given, shows, however, that in many respects the behaviour of an infected fasting rabbit differs from that of a dog and from that of man during pyrexia.

Below are given two tables showing complete results obtained with rabbit E (*cf.* p. 101) :

(*a*)

Body-weight.	Temperature.	External Temperature.	Output.					Remarks.
			Nitrogen in Urine.	Carbon in Urine.	Carbon in Expired Air.	Carbon from Proteid.	Carbon Nitrogen-free.	
—	39·5°	—	1·300	—	—	—	—	At end of first day.
2,530	39·2°	—	1·450	—	—	—	—	At end of second day.
2,430	39·5°	18·5°	1·790	1·424	13·22	5·796	8·848	At end of third day.
2,326	39·7° / 41·2°	18·8°	1·810	1·44	13·10	5·864	8·675	At end of fourth day.
2,213	40·8° / 40·7°	19·1°	2·450	1·95	14·55	7·938	8·545	At end of fifth day.
2,155	34·7° / 32·5°	18·5°	0·103	—	12.33	—	—	30 grammes of grape-sugar; collapse.

The first column gives the day of fasting, the second the mean weight of the animal, the third the mean external temperature, and the fourth the temperature of the animal, as in Table A. The three following columns give respectively the destruction of nitrogen, of carbon derived from sugar, and of carbon derived from fat. The next three columns

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express the last results in calories. Column 11 gives the total calorie production; columns 12 and 13 show the part taken by nitrogen-containing and nitrogen-free substances respectively in the total calorie production. Column 14 gives the calorie production per kilogramme body-weight, and column 15 the same per square metre of body surface.

(*b*)

Day.	Average Weight.	External Temperature.	Temperature of Animal.	Decomposed—			Calories—								Remarks.
				Nitrogen.	Sugar.	Fat.	Nitrogen.	Sugar.	Fat.	Total.	Nitrogen-holding.	Nitrogen-free.	Per Kg.	Per Square Metre.	
											Per cent.	Per cent.			
3	2,480	28·5°	39·2° / 39·5°	1·79	—	8·85	44·75	—	108·86	153·64	29·1	70·9	61·95	651	Normal day.
4	2,378	18·8°	39·7° / 41·2°	1·81	—	8·67	45·25	—	106·80	152·05	30·0	70·0	63·94	661	Commencement of fever.
5	2,270	19·1°	41·2° / 40·7°	2·45	—	8·54	61·25	—	105·12	166·37	36·3	63·2	73·29	746	Height of fever.

The fox-terrier infected with surra trypanosomes, which Stähelin employed for experiment, was fed upon Spratt's dog-biscuits (*cf.* p. 102). Analyses of the latter gave 90·72 per cent. of water; in the dried substance, nitrogen 4·05 per cent., carbon 45·10 per cent., hydrogen 6·81 per cent. Calorimetric examination with a Berthelot cylinder gave the value of 1 gramme dried substance at 4,604 calories.

The ratio C : N in the urine ranged, except during the last six days, between 0·732 and 0·758. The calorie value of the latter after drying (omitting the last six days) was 7·544 to 8·810 kilogramme-degrees per 1 gramme.

The fæces were dried, and their carbon, nitrogen, hydrogen, and calorie value determined. The fæces were checked by administering charcoal at the beginning of the experiment and at the time of inoculation. The fæces obtained during each (*A* and *B*) of these periods were collected separately. The following results were obtained:

	Period A.	*Period B.*
	Per Cent.	Per Cent.
Water	66·79	68·31
Nitrogen in dried substance	5·79	5·03
Carbon in dried substance	41·86	42·86
Hydrogen in dried substance.. ..	5·93	6·41
Calorie value per 1 gramme of dried substance	4,106 calories	4,209 calories

Table A gives the body-weight, the intake of food and water, the respiratory exchange, the urine and fæces, and also the nitrogen and carbon balance. The nitrogen content of the fæces is determined for the two periods, and allowed for each day. The amounts not absorbed, but retained in the fæces, were as follows:

	Period A.	*Period B.*
	Per Cent.	Per Cent.
Nitrogen of food taken	24·4	19·75
Carbon of food taken	17·5	15·5
Fat of food taken	13·2	15·5
Calorie value of food taken	16·8	15·1

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TABLE A.

Date.	Weight at Commencement.	Intake.		Output.		Respiratory Output.		CO_2.		H_2O.		Nitrogen Balance.				Carbon Balance.			
		Dry Food.	Water.	Urine.	Fæces.	CO_2.	H_2O.	Per Kg. Body-weight.	Per Square Metre (Surface).	Per Kg. Body-weight.	Per Square Metre (Surface).	Food.	Urine.	Fæces.	Balance.	Food.	Respiration.	Urine.	Fæces.
June 10, 11 -	8·58	140	140	135	(140·0)	174·8	98·7	20·37	350·5	11·50	200·5	5·67	4·09	1·38	+0·20	57·27	47·7	3·07	10·01
June 11, 12 -	8·51	140	360	128	53·0	208·9	182·2	24·56	421·3	21·41	367·5	5·67	4·23	1·38	+0·06	57·27	57·0	3·17	10·01
June 12, 13 -	8·64	140	140	98	84·0	207·4	142·5	21·69	374·0	16·49	284·4	5·67	3·88	1·38	+0·41	57·27	50·0	2·99	10·01
June 13, 14 -	8·56	140	140	111	82·0	174·5	121·8	20·38	350·3	14·22	244·5	5·67	3·64	1·38	+0·65	57·27	47·6	2·40	10·01
June 14, 15 -	8·63	140	140	131	—	172·0	104·2	19·93	343·6	12·07	208·1	5·67	4·12	1·38	+0·17	57·27	46·9	3·09	10·01
June 15, 16 -	8·62	140	140	126	116·0	176·3	101·0	20·45	352·4	11·71	201·8	5·67	4·31	1·38	−0·02	57·27	48·1	3·28	10·01
June 16, 17 -	8·46	140	140	119	100·0	166·5	127·2	19·68	337·0	15·03	257·4	5·67	4·35	1·38	−0·06	57·27	45·4	3·31	10·01
June 17, 18 -	8·35	140	140	117	—	166·2	110·7	19·90	339·3	13·26	225·9	5·69	4·46	1·38	−0·17	57·27	45·2	3·40	10·01
Total -	—	1,120	1,340	965	575·0	1426·6	988·3	—	—	—	—	45·36	33·08	11·04	+1·24	458·16	389·4	24·71	80·08
Average -	—	—	—	—	—	=178·6	=123·7	20·87	385·5	14·46	248·8						Balance—35·6		
June 18, 19 -	8·43	—	140	80	84·0	176·5	111·9	20·93	358·1	13·27	227·0	—	3·25	—	−3·25	—	48·1	2·65	—
June 19, 20 -	8·25	140	140	110	57·0	184·1	112·2	22·31	378·8	13·60	231·0	5·67	3·86	0·98	+0·83	57·27	49·2	3·15	7·70
June 20, 21 -	8·20	140	140	107	—	205·4	221·5	25·05	424·5	27·02	457·8	5·67	4·00	0·98	+0·69	57·27	56·0	3·26	7·70
June 21, 22 -	8·22	140	140	130	82·0	127·7	146·9	15·53	263·5	17·87	303·2	5·67	4·36	0·98	+0·33	57·27	34·8	3·55	7·70
June 22, 23 -	8·30	99	158	116	—	156·1	120·4	18·80	320·0	14·51	246·8	4·01	4·50	0·98	−1·47	40·51	42·5	3·66	7·70
June 23, 24 -	8·05	140	280	142	60·0	169·3	139·3	21·03	354·2	17·31	291·5	5·67	4·87	0·98	−0·18	57·27	46·2	3·96	7·70
Total -	—	659	998	685	283·0	1019·1	852·2	—	—	—	—	26·69	24·84	4·90	−3·05	269·59	276·8	20·23	38·50
Average -	—	—	—	—	—	169·85	142·0	20·61	349·8	17·265	292·2						Balance—65·9		
June 24, 25 -	8·16	140	280	140	86·0	186·4	147·4	22·84	386·5	18·06	305·6	5·67	5·09	0·98	−0·40	57·27	50·8	3·88	7·70
June 25, 26 -	8·16	140	280	135	95·0	197·4	136·1	21·74	367·9	16·67	282·1	5·67	5·15	0·98	−0·46	57·27	53·8	3·90	7·70
June 26, 27 -	8·27	140	280	177	—	231·6	208·1	28·00	475·8	25·17	427·7	5·67	5·75	0·98	−1·06	57·27	63·2	4·36	7·70
June 27, 28 -	8·17	140	280	200	191·0	235·6	176·7	28·84	488·2	21·63	366·1	5·67	7·49	0·98	−2·80	57·27	64·3	5·48	7·70
Total -	—	560	1,120	652	372·0	851·0	668·3	—	—	—	—	22·68	23·48	3·92	−4·72	229·1	232·1	17·62	30·80
Average -	—	—	—	—	—	206·75	167·1	25·36	429·6	20·38	354·4						Balance—51·4		
						Per day													

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June 28, 29 -	8·24	140	140	156	—	229·0[1]	172·0[2]	27·79	471·8	20·87	354·3	5·67	7·18	0·98	−2·49	57·27	62·5	5·26	7·70
June 29, 30 -	7·95	140	140	157	89·0	229·0[1]	190·0[2]	28·80	483·1	23·90	400·9	5·67	5·33	0·98	−0·64	57·27	62·5	3·90	7·70
June 30 to July 1 -	7·95	140	280	167	—	229·0[1]	214·0[2]	28·80	483·1	26·92	451·4	5·67	6·75	0·98	−2·06	57·27	62·5	4·97	7·70
July 1, 2 -	7·87	140	280	168	105·0	229·0[1]	232·0[2]	29·09	486·4	29·47	492·8	5·67	5·99	0·98	−1·30	57·27	62·5	4·41	7·70
July 2, 3 -	7·81	84	201	168	—	229·0[1]	181·0[2]	29·32	488·9	23·17	386·5	3·41	5·63	0·98	−3·20	34·36	62·5	4·14	7·70
July 3, 4 -	7·71	47	283	170	52·0	229·0[1]	239·0[2]	29·70	493·0	30·90	514·6	1·90	5·51	0·98	−4·59	19·23	62·5	4·17	7·70
July 4, 5 -	7·65	64	249	123	—	229·0[1]	193·0[2]	29·39	495·7	25·23	417·8	2·59	4·81	0·98	−3·20	26·18	62·5	3·58	7·70
Total -	—	955	1,573	1,109	246·0	1603·0	1421·0	—	—	—	—	30·58	41·20	6·86	−17·48	308·85	437·5	30·43	53·90
Average -	—	—	—	—	—	229·0	203·0	29·06	486·0	25·79	431·2						Balance—213·4		
						Per day													
July 5, 6 -	7·65	100	320	179	202·0	222·4	187·7	29·07	481·5	24·53	406·2	4·05	4·60	0·98	−1·53	40·91	60·7	3·42	7·70
July 6, 7 -	7·55	100	100	209	—	194·4	266·6	25·72	424·5	35·32	582·2	4·05	5·88	0·58	−2·41	40·90	53·0	5·74	3·3 (?)
July 7, 8 -	7·35	50	250	203	—	169·7	155·7	23·09	377·8	21·18	346·1	2·025	5·08	0·58	−3·635	20·45	46·3	4·96	4·3 (?)
Total -	—	250	670	591	202·0	586·5	610·0	—	—	—	—	10·125	15·56	2·14	−7·575	102·27	160·0	14·12	136 (?)
Average -	—	—	—	—	—	195·5	203·3	25·96	427·8	27·01	444·8						Balance—86 (?)		
						Per day													
July 8, 9 -	7·23	50	250	301	86·0[3]	174·2	130·2	24·09	391·5	18·01	292·6	2·025	8·62[6]	0·58[6]	−7·275	20·45	47·5	7·67	7·8
July 9, 10 -	7·00	—	145	105 (?)	229·0[4]	146·7	115·4	20·96	337·0	16·48	265·1	—	3·59	2·59[7]	−6·18	—	39·0	4·72	7·5 (?)
July 10, 11 -	6·64	—	97	135 (?)	159·5[4]	134·4	130·8	20·33	320·7	19·79	312·0	—	2·53[7]	0·69[7]	−3·22	—	36·7	3·33	3·1 (?)
July 11, 12 -	6·34	—	—	40 (?)	—	123·4	167·8	19·46	302·8	26·46	411·7	—	3·37(?)	—	−3·37	—	33·7	4·4 (?)	(?)
													1·13						
12 until death (about ten hours)	6·09	—	—	240[5]	—	66·6	71·8	26·23	402·7	28·30	434·2		0·14		−1·27	—	19·6	—	4·9
	5·74 (post-mortem)							Twenty-one hours' estimation.				(Stomach contents of cadaver.)							
	—	50	482	821	474·0	—	—	—	—	—	—	2·025	18·61	4·63	21·215	20·45	76·5	20·12	23·3

[1] Average between June 27 and 28 and July 5 and 6.
[2] Calculated from CO_2 and the found relations of H_2O to CO_2 in the ventilations air.
[3] Vomited.
[4] Mixed with urine.
[5] Mixed with fæces and vomit.
[6] Mixed with vomit.
[7] Urine and fæces.

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To enable a correct idea to be obtained of the excretion of CO_2, which possesses a different significance according as it arises from protein, fat, or carbohydrate, the destruction of the individual food-stuffs was calculated, and is given in Table B.

This calculation was rendered the more simple owing to the circumstance that the amount of destruction, as is shown by the nitrogen and carbon deficit, always exceeds the intake. Stähelin was able, by previously abolishing the store of glycogen in the body, to ensure that the increased output of carbon was derived from body protein and body fat. The amount derived from protein can be calculated from the nitrogen deficit. Since, in proteid destruction, one part of nitrogen corresponds to 3·2 parts of carbon, it is necessary to subtract from the carbon output the nitrogen deficit multiplied by 3·2 in order to obtain the amount of carbon which is derived from the body fat.

Since, according to Rubner, 1 gramme nitrogen derived from the destruction of body protein corresponds to 25 calories, while 1 gramme carbon derived from fat corresponds to 12·31 calories, it is easy to determine how many calories are produced by destruction of protein and fat respectively. To this must be added the calorie value of the food, which was determined directly, while the calorie value of the urine and fæces, also directly determined, must be subtracted. In this way the total heat-production is determined.

In judging the amount of heat-production, Stähelin took into account the value per unit of body-weight and also per unit of body surface. The latter was calculated from Meeh's formula, employing 11·9 as the constant.

In the preliminary period the heat-production per kilogramme of body-weight amounted to 59·81 calories, and per square metre of body surface 1,027 calories, the latter being in agreement with the recognised mean for the dog (1,030 calories).

During the two days following inoculation the heat-production remained practically unchanged. On June 20 to 21 an increase to 83·79 calories per kilogramme (1,245 per square metre) occurred without any rise of body temperature. Stähelin is, however, inclined to attribute this result to an error of experiment. During the next two days the output of heat further increased, reaching again on June 24 to 25 the normal value. During this time irregular elevation of body temperature up to 39·5° C. occurred. This diminution of heat-production during the onset of fever, or during the incubation period, corresponds to the older observations of Senator. From June 25 to 28 during high fever the heat-production increased still more, reaching 88·88 calories per kilogramme and 1,507 calories per square metre, or 47·4 and 45·3 per cent. respectively. For the period from June 28 to July 5 a mean heat-production of 83·71 calories per kilogramme and 1,404 calories per square metre was found, the calculation being based upon the CO_2 values (the mean of the two preceding and the two following days). The loss of water can be reckoned from the food consumption (see below) and compared with that directly measured. During this period a fair agreement was obtained, the difference amounting to only 35 grammes.

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TABLE B.

Date.	Food Calories.	Calories from Tissue Exchange.		Total.	Heat-production (after Deduction of Calories in Urine and Fæces).	Albumin during Decomposition yields—		Calories from Water Loss.	Calories from Conduction and Reduction.	Heat Loss through Evaporation.	Calories per Kg.	Calories per Square Metre.	Temperature.	
		From Albumin.	From Fat.			As Calories.	In Per Cent.			Per Cent.			Evening.	Morning.
June 10-18 - (Average.)	585	−4·00	61·55	642·05	510·0	103·4	20·3	74·1	518·9	14·3	59·80	1,027	—	—
June 18, 19 -	—	81·25	496·70	577·90	549·9	81·2	14·8	67·1	482·8	12·2	65·24	1,116	38·1	37·9
June 19, 20 -	585	−2·70	66·90	631·10	525·0	96·5	18·4	67·3	457·7	12·4	63·63	1,081	37·9	37·9
June 20, 21 -	585	−1·72	269·60	837·30	687·0	100·0	14·6	132·7	554·3	19·3	83·79	1,425	38·3	38·0
June 21, 22 -	585	−8·30	−121·90	454·80	341·4	109·0	31·9	88·1	253·3	25·9	41·54	705	38·2	38·0
June 22, 23 -	413	36·75	91·10	540·80	425·1	112·5	26·5	72·2	352·9	17·0	51·22	872	38·7	38·1
June 23, 24 -	585	4·50	−2·40	587·10	469·3	121·7	25·9	83·6	385·7	17·8	58·30	982	38·3	39·4
June 24, 25 -	585	10·00	46·70	641·70	521·4	127·5	24·5	88·4	433·0	17·0	63·89	1,081	39·5	38·3
June 25, 26 -	585	11·50	81·20	677·70	556·9	128·2	23·0	81·7	475·2	14·7	68·25	1,154	37·7	39·6
June 26, 27 -	585	26·50	179·70	791·20	675·2	143·2	21·2	24·9	550·3	18·5	81·64	1,388	40·1	39·6
June 27, 28 -	585	70·00	206·60	861·60	729·3	187·5	25·7	106·0	623·0	14·5	88·88	1,507	39·2	37·9
June 28 to July 5 - (Average.)	451	62·50	276·00	790·50	665·2	147·2	22·1	121·8	543·4	18·3	83·71	1,404	—	—
July 5, 6 -	418	37·20	319·80	775·00	658·8	115·0	17·5	112·6	546·2	17·1	86·68	1,432	38·5	39·9
July 6, 7 -	418	60·20	165·00	643·00	527·0	147·0	27·9	160·0	467·0	30·4	69·81	1,150	39·8	40·4
July 7, 8 -	209	90·90	277·00	577·00	482·0	127·0	28·4	93·4	389·0	19·4	65·57	1,070	39·4	39·5
July 8, 9 -	209	179·40	252·00	640·00	553·0	198·0	35·8	78·1	465·0	14·1	76·49	1,240	38·2	38·8
July 9, 10 -	—	154·50	387·00	541·00	391·0	140·0	35·8	69·2	322·0	17·7	55·86	900	37·7	36·4
July 10, 11 -	—	80·50	404·00	484·00	384·0	73·0	19·0	78·5	306·0	20·4	58·09	920	36·4	36·5
July 11, 12 -	—	84·20	337·00	421·00	366·0	84·0	23·0	100·7	265·0	27·2	57·73	900	35·5	35·9
July 12, 13 -	—	76·20	600·00	667·00	650·0	25·0	3·8	100·0	550·0	15·0	105·00	650	—	—

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On July 5 to 6 the heat-production per kilogramme body-weight was approximately the same as on June 27 to 28—namely, 88·68 in place of 88·88—while the amount per square metre was less—namely, 1,432 in place of 1,507. Compared with the normal, these increases amount to 44·9 and 39·4 per cent. respectively. A fall then occurred, followed by a transitory rise on July 8 to 9, after which subnormal values were obtained.

Having regard to the metabolism and temperature during the last days of experiment, and the loss of body-weight and of nitrogenous constituents, the conclusion might be drawn that death was the result of inanition. This is, however, contradicted by the composition of the organs after death. Analysis yielded the following results:

		Per Cent.
Muscle	Dried substance	25·52
	Nitrogen of dried substance	11·96
	Fat	22·32
Liver	Dried substance	24·02
	Nitrogen of dried substance	11·45
	Fat	12·14

In calculating heat-production Stähelin makes two assumptions:

1. That only protein and fat derived from the body of the animal experimented upon are burnt off. This assumption is not strictly true, since glycogen is of course also burnt off. Nevertheless the error introduced is inconsiderable.

2. That protein and fat, disregarding what is lost in the urine and fæces, are burnt off to end-products, no intermediate products remaining behind in the body. Respecting such retention, see below. In this assumption at the most a slight error is introduced.

The amount of the heat-production which is employed in warming the body itself can be disregarded. More important is a correction arising out of the dependence of metabolism upon body temperature. If the value given by Frank and Voit for the increase of CO_2 output for each rise of temperature of one degree—namely, 7 per cent.—is adopted, and this correction added to the heat-production of the preliminary period, the following figures, permitting of comparison with the actual results, would be obtained:

	Calories per Kilogramme.	*Calories per Gramme.*
36° C.	52·2	897
37° C.	55·9	960
38° C.	59·8	1,027
39° C.	64·1	1,099
40° C.	68·6	1,176

If these figures are compared with those which obtain during fever, it will be seen that on three days in particular—namely, June 26 to 27, June 27 to 28, and July 5 to 6—a very marked increase was observed. The question arises how much of this increase proceeds from protein. If the fraction of the heat-production which is due to protein be subtracted, the following figures result:

	Per Kilogramme Body-weight.	*Per Square Metre.*
June 26 to 27	78·91	1,342
June 27 to 28	81·77	1,358
July 5 to 6	82·51	1,363

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The particularly reliable observations on July 5 to 6, on which occasion the mean temperature was 39·2° C., show a very considerable increase above the amount corresponding to 39° C. Stähelin, however, regards it as undesirable to subtract in this way the heat-production derived from increased destruction of protein, because the heat thus set free preserves an isodynamic amount of fat from oxidation, this amount being, however, diminished by a quantity corresponding to the specific dynamic action of the protein broken down. A measure of the part played by increased protein cleavage in the augmented heat-production is afforded by calculating the percentage amounts in which protein enters into heat-production. Stähelin has given these amounts in Table B, from which it is seen that protein takes a somewhat larger share in total heat-production than during the preliminary period, but that this increase does not become obtrusive until the period of falling temperature is reached. Consequently we must conclude, with Stähelin, that during the days on which a marked increase of metabolism occurs an increased destruction of fat accompanies the increased protein destruction.

The distribution of the loss of heat into that dependent on the evaporation of water and that taking place by convection and radiation may be calculated when it is borne in mind that the evaporation of 1 gramme of water requires a mean amount of 600 calories. The amount of water evaporated is made up of that given off by the lungs and that from the skin. The following mean values were obtained :

	Grammes per Kilogramme of Body-weight.	*Grammes per Square Metre of Surface.*
Preliminary period	14·46	248·8
Incubation and prodromal period	17·27	292·2
First period of fever	20·38	345·4
Second period of fever	25·79	431·2
Third period of fever	27·01	444·8
Final period	20·18	320·3

It will be seen that the evaporation of water increases even in the early period of infection, because more marked during the period of fever, and declines somewhat during the final period. The actual loss of heat from evaporation of water is given in Table B. Taking into consideration all sources of error, Stähelin concludes that the distribution of the output of water in the various modes in which this may occur is not materially altered during fever, and this agrees with the experience of other observers.

At the end of his valuable work Stähelin summarizes the total body destruction of the animal experimented upon as follows :

	Protein Destruction.	*Fat Destruction.*	
Preliminary period	8	51	
Incubation and prodromal period	17	73	
First period of fever	29	49	
Second period of fever	110	204	
Third period of fever	47	79	
Final period	143	175	
Total loss of weight			2,840
Loss of body substance			960
Loss of water			1,880

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Intake and Output of Water.

Water drunk	6,200
Water contained in dog-biscuit	315
Water derived from oxidation of food (that from hydrogen in urine and fæces being subtracted)	1,625
Water derived from oxidation of body protein	210
Water derived from oxidation of body fat	680
Total intake	9,030
Water in urine	4,530
Water in fæces	1,540
Water expired	5,155
Total output	11,225
Difference between intake and output	2,195
Calculated from loss of substance	1,880

The experiments of May and Stähelin are in agreement in showing that in fever an increased heat-production may occur. Stähelin finds that oxidative processes generally are increased, and that fat destruction also takes part in this increase. One of May's experiments, at least, showed also a marked combustion of fat, and a tendency in the same direction was exhibited by other rabbits. It cannot, therefore, be contended that in infective fevers (toxic) protein destruction is exclusively responsible for the increased heat-production. Judging from the numerical differences of the results obtained by May and Stähelin, it appears probable that individual infective processes exhibit variations, and exert a specific influence upon metabolism. The strongest and most extensive effect is to be expected in those cases of fever in which the most rapid failure of strength is known to occur. It must, however, not be forgotten that, assuming that the increased oxidation affects protein metabolism alone, a diminution of the amount of fat occurring during long-continued fever would be quite explicable as due to inanition, this again being, as von Noorden has pointed out, the result of loss of appetite and the altered diet of fever. It is now, however, no longer possible in any case to attribute the fat consumption in fever exclusively to inanition.

Krehl and Soetbeer have made the important observation that in infected cold-blooded animals oxidative processes are increased, though no rise of body temperature occurs. This increase must, therefore, be due to toxines produced in the infective process, and cannot be attributed to febrile pyrexia. Additional proof is thus afforded of the mutual independence of pyrexia and oxidative processes.

In man during fever the consumption of oxygen and output of carbon dioxide are shown by determinations of the respiratory exchange to be more or less considerably (20 to 70 per cent.) increased [Kraus, A. Loewy, Riethus, Svenson]. Nevertheless, cases are met with in which no deviation from the normal occurs [Kraus, Loewy], or, at least, only a slight decrease [Kraus, Robin, Binet]. In a considerable majority of cases, however, oxidation as determined by the gaseous exchange is—at any rate, during the height of acute fever—increased. According to our own observations, increases of 50 to 70 per cent. are referable to

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accompanying muscular action. F. Müller thinks that increased oxidation caused by rigors, by accelerated rate of respiration, and by exalted cardiac action, are to be attributed to fever, since they are brought about by processes constituting febrile symptoms. The same author regards these muscular actions as to a certain extent furnishing the means by which the increased oxidation is brought about; it seems that, in addition to physical heat regulation, chemical thermotaxis comes into play when increased muscular action is brought about by impulses proceeding from the nervous system. As a matter of fact, no objection can be urged against such chemical regulation. It must be pointed out that, when an attempt is made to estimate the value of the determining factors of gaseous exchange without taking note of such muscular activity, differences of result appear, which do not seem to be really essential, since rigor and acceleration of pulse and respiration are "individual" factors. We are also of opinion that in chemical heat-regulation the maintenance of absolute muscular rest is of importance. According to Rubner, rigor and shivering certainly lie outside the range of this form of thermotaxis. Stähelin points out that his dog habitually lay down and remained quite still, so that muscular action, calculated of itself to cause an elevation of temperature, was excluded; in particular during the illness careful observation failed to reveal any increased muscular action. Without this how would it have been possible to compare directly the results obtained during the fever period with those yielded by the preliminary period? We must also urge that an attempt should be made to subtract from the gross oxygen consumption observed in human beings suffering from fever an amount corresponding to visible muscular action, and also an amount answering, according to the accepted teaching of Pflüger, to the pyrexial state. If this is done, a net value remains which, on the average, is not very high. In opposition to this, Speck asserts that there is no proof that in fever heat-production is increased, apart from the rise due to muscular action, which he regards as accidental, and to which he attributes the increased oxidation observed. We are, however, unable to follow him, just as we also cannot agree with the conclusions of another competent observer, L. Krehl. In any case, there is in man no direct parallelism between degree of pyrexia and amount of oxidation, as has recently been shown by Riethus. Many infective processes run their course with marked increase of oxidative metabolism in spite of a quite inconsiderable rise of temperature. In no case can the febrile rise of temperature be the result of increased oxidation, for the increase of the determining factors of the gaseous exchange never reaches in fever the amount obtaining in excessive muscular exertion, during which the body temperature, as is well known, remains normal. In estimating the consumption of energy by patients in the later stages of febrile infection, assistance is rendered by a knowledge of the diet upon which for periods of not less than two to three weeks the body-weight is maintained unchanged. Von Noorden has made many observations of this kind during the later stages of prolonged typhoid fever, and also in septicæmia and pulmonary phthisis. The observations were made on female adults whose nutritional condition was very considerably reduced.

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The following are the lowest figures he obtained :

	Weight.	*Total Daily Calorie Output.*	*Daily Calorie Output per Kg. of Body-weight.*
	Kg.		
Typhoid fever	48	1,200	25
Tuberculosis	44	1,010	23
Chronic septicæmia ..	43	1,030	24
„ „ ..	40	1,000	25

All von Noorden's cases had a temperature exceeding 38·5° C., and preserved their weight unchanged for at least two weeks, receiving a diet rather rich in protein. Von Noorden usually obtained somewhat higher figures—namely, 25 to 30 calories per kilogramme—with patients suffering from chronic febrile diseases whose body-weight remained constant. On the other hand, he met with cases in which the body-weight remained constant when the food appeared to yield only 17 to 19 calories per kilogramme. In such cases œdema always appeared soon after the termination of the period of observation. Obviously the body-weight appeared to be unchanged because an accumulation of fluid, incapable of recognition, was occurring, the body substance meanwhile being in reality diminished.

The low calorie values of 23 to 25 per kilogramme show that in the later course of fever the body cells work less, and thus diminish the evil effect of loss of appetite and diminished intake of food. Only in this way is it possible to explain the circumstance that patients suffering from chronic fever at first lose considerably in weight, subsequently preserving their weight unchanged for weeks or months upon a strikingly small diet.

We pass now to the respiratory coefficient in fever. Regnard asserted that in febrile conditions the relation of the carbon dioxide eliminated to the oxygen taken up diminished, and concluded from this that oxidation was inhibited during fever, thus leading to an accumulation of intermediate metabolic products in the tissues, and to a lowering of the respiratory coefficient to 0·6 or even to 0·5. Finkler obtained similar low values for the respiratory coefficient in febrile animals, as also May in rabbits, Riethus in man, and A. Loewy in dogs, in which he had excited a febrile pneumonia by injecting silver nitrate into the lungs. Loewy concluded that carbon was eliminated otherwise than by the lungs, and in a different form of combination. From our own experiments on fever in man we concluded that the respiratory coefficient is uninfluenced by febrile states as such, but is determined by the existing nutritional state, by the bodily condition, and by the material available for metabolism. The observations we have since made have confirmed this opinion. Quite recently Jaquet has adopted the same view, and has shown that a diminution of CO_2 elimination in respired air may depend upon a diminished respiratory effort, and less complete ventilation of the lungs.

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The extent to which carbohydrates are broken up in fever is at present very incompletely ascertained. In the older literature statements concerning the metabolism of glycogen, and its disappearance from the organs in fever and allied conditions, are to be met with. Manassein, describing his own experiments, came to the conclusion that glycogen was considerably diminished in, or even disappeared from, the liver of the rabbit during fever. It is true he was unable to decide whether this diminution of glycogen was to be attributed to the existing inanition, or whether it depended directly on the fever or on the cause of the fever. Having regard to the fact, which had at that time become recognised and was the subject of much discussion, that the elimination of sugar in diabetes often disappeared during fever, he inclined to the view that this diminution of sugar was not due exclusively to starvation. We now know that glycogen is rapidly destroyed in fever, and that during fever the store of glycogen becomes scanty. Richter was the first to show that in the rabbit the glycogen of the liver becomes diminished after puncture of the heat-regulating centre.

May believed he had shown, in his experiments on rabbits during fever, that administration of carbohydrates reduced protein destruction to, or even below, the normal amount. He therefore concluded that the increased protein metabolism of fever is due to want of carbohydrates rather than to protoplasmic poisoning. Apart from a possible influence of the diet taken, May attributed the want of carbohydrates to an increased capacity of the body cells during fever to destroy glycogen. The fact that after feeding with sugar the liver of febrile animals was considerably poorer in glycogen than was the liver of healthy control animals appeared to May to support the view he held. Against this, however, is the circumstance that the muscles were somewhat richer in glycogen. The liver did not lose under the influence of pyrexia the power of forming glycogen, but either the glycogen which was formed was more rapidly used up, or a considerable amount of the sugar taken became burnt off without previously becoming transformed into glycogen.

It is indeed true that under physiological conditions protein destruction increases when a considerable amount of the carbohydrates is omitted from an otherwise abundant diet. The organism is then in a condition of partial deprivation of food, and, in order to supply its needs, draws upon the tissue-protein in addition to the store of carbohydrate and fat [Miura, Lusk, von Noorden, F. Voit, and Kayser]. But while only a relatively small amount of protein is saved from destruction by augmenting nitrogen-free food-stuffs, the opposite is equally true, for if the latter are suddenly cut off only a small amount (according to Magnus-Levy, 7 to 17 per cent.) of the energy deficit is covered by drawing upon body protein, the greater part being provided by the destruction of the store of glycogen and of body fat. Now, in fever the increase of oxidative processes is, on the whole, inconsiderable, remaining much behind that of men using considerable muscular exertion, in whom the extensive destruction of carbohydrate does not require to be supplemented by an increase of the nitrogen output. Moreover, the increased destruction of protein in fever is not generally so much diminished by the administra-

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tion of carbohydrates as May asserts. Consequently May's arguments lose much of their force. The relative richness in glycogen of the muscles, compared with the poorness of the liver, admits of a natural explanation, when it is assumed that a migration of glycogen, dictated by the needs of the organism, takes place.

Hirsch, O. Müller, and Rolly have recently reinvestigated the part played by glycogen in febrile processes. Employing a thermo-electrometer adapted for thermo-electric measurement of temperature, these authors found that, in warm-blooded animals, the liver, both normally and in pyrexial conditions due to infection or to puncture of the heat-centre, always exhibited a higher temperature than the blood, the muscles, and the skin. Pyrexia due to puncture makes its appearance also in curarized animals. It follows that the muscles here take but little share in heat-production. Hirsch, Müller, and Rolly conclude that the liver takes a large share in normal and febrile heat-production because of its higher temperature, and in the same way assume that an increased destruction of that substance which is principally stored up in the liver—namely, glycogen—takes place. The significance of glycogen is, however, not the same for all forms of pyrexia. It is essential only for pyrexia following puncture, for if the animals are made completely glycogen-free, both for liver and muscles, injury of the so-called heat-centre in the corpus striatum produces no rise of temperature. If the organs of the glycogen-free animal are again made to contain glycogen by administering sugar, they again react to puncture. In infective fevers the case is different. Pathogenic organisms and their toxines cause pyrexia in rabbits whether these are glycogen-free or not. The presence of glycogen is, therefore, not essential to pyrexia in infective fevers. Consequently the material destroyed must be different in the two cases. After puncture, an increased destruction of carbohydrate leads to the rise of temperature, which in its turn leads secondarily, in this as in all forms of pyrexia, to increased protein destruction. In infective fever, on the contrary, both an abnormally high protein disintegration and also an increased consumption of nitrogen-free carbohydrate occurs. In fever two processes of like origin proceed in company—a specific destruction of protein, which has been injured by albuminoid protoplasmic poisons, by means of hydrolysis, and a central impulse, as in puncture of the heat-centre. Hirsch and Rolly again point to the rapid disappearance of liver glycogen and the cessation of glycosuria in diabetes during fever as an argument for assuming an increased destruction of nitrogen-free material. Both conditions stand, according to Hirsch and Rolly, in causal relation. The specific protein destruction might, in fact, occasion central chemical stimulation, as in puncture of the heat-centre. Rolly then investigated protein cleavage, both in febrile animals and in glycogen-free rabbits after puncture. In the first pyrexia was attended with a considerably increased nitrogen elimination; in the trephined animals, on the contrary, protein metabolism was unaffected.

Future investigation of the fundamental problem of the pathology of fever must take note of the interesting work of Hirsch and Rolly, which, however, has, it must be admitted, been received with much

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hesitation. Aronsohn has already published his objections, and Senator and P. F. Richter have submitted the work in question to unfavourable criticism and to a partial reinvestigation.

Hirsch and Rolly, in opposition to Rubner's opinion that the importance of the thermo-chemical aspect of glands may easily be overestimated, maintain, in harmony with the older views, that the intensity of the metabolism of an organ is to be estimated by the share it takes in heat-production. As, however, these two authors do not make a sharp distinction between increased local warmth and increased heat-production, Rubner and most other observers are unable to relinquish their point of view. The question whether the gland cells and adjacent structures are subjected, during febrile states, to a pathological stimulation causing increased production of heat, while, by way of compensation, the muscles are partly thrown out of action, can only be settled by a consideration of the total febrile metabolism and energy production, not by mere observations on heat topography. The development of pyrexia after puncture of the heat-centre in a curarized animal forms, unfortunately, a weighty and as yet unanswered argument against Aronsohn's views. The problem whether pyrexia caused by puncture is directly due to a simple increase of carbohydrate destruction, and the accompanying increase of protein metabolism brought about as a secondary result of the rise of temperature, is regarded by Rolly as easily settled, for no rise of temperature was to be noted in his glycogen-free animals after trephining, and protein metabolism also remained unaffected. If, now, puncture of the heat-centre led to increased protein metabolism, it would be connected causally with the resulting rise of temperature. Unfortunately, here again the observations made are opposed to those of Senator and Richter (see below). Richter could not confirm the statement that when the store of glycogen was deficient or absent a rise of temperature was not observed in the rabbit after puncture of the corpus callosum. In the first case, when the animal had been starved and a small amount of glycogen still remained in the muscles, he did, in fact, observe an almost unchanged temperature. Nevertheless, when, by means of starvation and strychnine, the glycogen was completely removed, puncture was followed by a positive result, though the pyrexia was not so constant nor so marked as it would otherwise have been. When, moreover, in a glycogen-free animal, pyrexia does not follow cerebral puncture, or a fall of temperature results, it must be considered that in such a case the animal is in a very feeble state, scarcely able to support life. But few of Rolly's animals survived the preparatory treatment: deprivation of food for three days, combined with strychnine tetanus, would seriously affect all vital functions. Consequently it does not seem to be established that the rise of temperature is essentially dependent upon the presence of glycogen in the body. Rolly, moreover, observed gradations of difference when normal or glycogen-free animals were inoculated. The degree of rise of temperature of starved glycogen-free animals, after the introduction of virulent or dead bacteria, is not markedly lower than when inoculation of well-nourished animals is made. The disappearance of glycogen in fever, which was pointed out by Manassein, and again

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emphasized by Hirsch and Rolly, is, according to L. Mohr, by no means invariably the case. Fever may, indeed, increase diabetic glycosuria. Febrile alimentary glycosuria and pancreatic diabetes throw further light on the matter. Bacterial excitants of fever influence, as such, experimental glycosuria independently of the degree of pyrexia actually attained—thus streptococci cause disappearance of glycosuria, while anthrax produces no lowering of glycosuria, in spite of marked rise of temperature. It must be admitted that Senator and Richter are right when they urge that the increased destruction of no single substance can be asserted to stand in causal relation to rise of temperature. The present section shows that this is so. By merely overfeeding with protein, Rubner was able to increase the heat-production of the dog in the proportion of 100 to 160—and this relation can be many times increased by muscular action—but, nevertheless, no rise of temperature occurred. And even in fever itself an increased destruction is not constant. Respecting the increased breaking down of protein, the account given by Aronsohn and Sachs, Girard and Schultze, should be referred to. The results of these authors have recently been confirmed by Senator and Richter.

In the meantime, it may be stated in general terms that the production of pyrexia in animals is not associated unconditionally with the glycogen content of the organs. Fasting animals, possessing but little glycogen, react well both to puncture of the heat-centre and to infection, as do glycogen-free animals.

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5. The Alleged Retention of Water in Fever.

The question whether water is retained in fever, which is closely connected with the old theory of the crisis, must be sharply separated from the disturbance of certain processes having to do with the output of water.

The conjecture that patients during fever store up water in their tissues has for the most part arisen from the scanty excretion of urine. As a matter of fact, the amount of urine in typhoid, for example, is often diminished during the height of the fever, while during recovery the flow is suddenly or gradually increased. Again, during a temporary fall of temperature an increased diuresis sometimes appears. Rigors, according to Glax, usually cause a sudden rise in the secretion of urine, which afterwards rapidly subsides. In all probability this diminution of diuresis in fever is dependent upon feeble cardiac action and low blood-pressure; if the circulation is good, and a proper quantity of fluid is taken, we are confident, from our own clinical experience, that the elimination of water by the kidneys is not at all, or only very slightly affected.

From Rubner's investigations, in particular, we know that during increased heat-production in the organism, whatever its cause may be, the body, in addition to marked loss of heat by conduction and radiation, evaporates an abundant amount of water from both the lungs and skin, numerous factors influencing the preponderance of one or the other of these two modes of evaporation. According to the observations of Rubner, Wolpert, and Zuntz, the amount of water evaporated exhibits, when the heat-production is raised, a greater percentage increase than does the output of water by conduction and radiation. The evaporation of water by the skin is, especially in man, even with moderate heat-production, greater than by the lungs, and is capable of still greater increase. In the various stages of fever the evaporation of water appears to be modified in a characteristic manner, and does not take its normal share in the output of heat. In attempting to explain the pyrexia, account must be taken of the insufficiency of the evaporation of water.

Apart, however, from such variations in the output of water, which are concerned purely with heat regulation, and will be more fully considered later on, a complete insight into the relation of the intake and output of water during fever can only be obtained by sufficiently extended observations of total metabolism and consumption of energy, every aspect of the output of water, particularly diuresis and perspiration, being con-

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sidered in common with the energy consumption. Only when this is done are we in a position to talk of an insufficiency of elimination of water in fever resulting in retention of water in the organism.

In reference to this point, the intake and elimination of water by Stähelin's dog infected with surra is again given :

Water drunk	6,200
Water in dog-biscuit	315
Water produced by oxidation of food	1,625
Water produced by oxidation of body protein	210
Water produced by oxidation of body fat	680
Total intake	9,030
Water in urine	4,530
Water in fæces	1,540
Water in respired air	5,155
Total output	11,225
Difference between intake and output	2,195
Calculated from metabolism	1,880

The distribution of the heat output in different categories was in this dog not markedly different from the normal.

In this experiment there is obviously no question of retention of water. Whether Sahli's view that, in long-continued febrile affections, such as typhoid fever, for example, the tissues become poor in water can be accepted without qualification is uncertain. It seems permissible, from the behaviour of animals in respect of output of water, which, so far as perspiration is concerned, is effected through the lungs, to draw conclusions respecting the evaporation of water by the skin in man.

As is well known, Herz advanced the hypothesis that one of the most important sources of heat in fever, not revealed by chemical investigation of metabolism, is a toxic combination with water on the part of the cell-protoplasm. This swelling of the cell-protoplasm must be of a special character, for ordinary molecular imbibition is a process in which work is done and heat disappears; nevertheless, other investigations show that in febrile states the possibility of abnormal combinations with water in the cell liberating heat cannot be excluded. The final argument for assuming the existence of such swelling of cell-protoplasm is, in any case, the alleged retention of water in fever.

Herz has now asserted that at any rate the blood cells in fever really undergo an acute swelling. Moreover, the fluid content of the blood is, according to E. Grawitz, changed by every marked movement of lymph, and therefore by the assumption of water by large glandular organs or systems of organs. Pfeiffer has made in our laboratory a number of determinations of the volume of the blood cells of man in febrile states, employing for this purpose Bleibtreu's method. Eight individuals with different affections (malaria, acute tonsillitis, rheumatic fever, pneumonia) were selected; in five venesection was performed at the height of the fever (axillary temperature 39·1° C. to 40·3° C.), and repeated when the temperature had fallen 2° C. to 3° C., either spontaneously (malaria) or following the administration of antipyretics (antifebrin, antipyrin).

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In reality, during fever the volume of the plasma and the size of the individual erythrocytes do not exhibit any considerable deviation from the normal. The volume of the serum is normally 44 to 66 per cent. that of the blood; in marked fever 48 to 77 per cent. was observed. The normal volume of the individual red cells is 820×10^{-10} c.mm. to 966×10^{-10} c.mm.; during high fever the volume ranged between 675×10^{-10} c.mm. and 948×10^{-10} c.mm. The number of the red blood cells was found to be almost unchanged in the cases examined. A different result was obtained by the application of external cold; in this case an actual concentration of the blood occurs [Winternitz, Knöpfelmacher]. These results run counter to the view that the blood is a tissue, whose formed elements can be shown with tolerable regularity to enter into combination with water during the height of fever. The passage of fluid from the blood to the tissues, which is brought about by the cold bath in patients suffering from fever just as in healthy people, is not a simple reversal of an analogous process of opposite character from the tissues to the blood; it is rather a stimulation effect proceeding from the skin, and comparable with contraction of almost all the vascular areas of the larger circulation resulting from powerful stimulation of the medulla. The possibility of the explanation just given being correct possesses a certain significance in respect of the theory advanced in Section 6.

For our further knowledge of the elimination of water from the skin of man in febrile conditions we are chiefly indebted to the researches of Krehl's pupils, especially to G. Lang. Previously determinations of the output of heat due to elimination of water had been carried out by Nebelthau on rabbits, and by Krehl and Mathes on rabbits and guinea-pigs. They found that when the output of heat due to elimination of water in fever increases, the output due to evaporation preserves the normal relation to that due to conduction and radiation—a result which, judging by the results of Rubner and Wolpert, given above, appears to be somewhat pathological. Apart from a dissertation in Russian by Wassilewski, which has remained unnoticed, no exact data respecting the total output of water by the skin in man during fever were available. Further, the number of estimations of the total amount of water given off by the skin and lungs together during pyrexia was small. In Lang's observations a rise of temperature was produced by injecting tuberculin. Unfortunately his experiments are of but short duration. When the body temperature is normal, the hourly elimination of water by the skin per square metre of surface amounts to about 13 grammes. During continued fever the output is about the same. The output of heat by evaporation of water from the skin would, according to this, not be increased in fever. The pathological aspect of this relation seems particularly striking when a comparison is made with the output of water of the same subjects, with a normal temperature, two to three hours after taking food. The output after a meal whose heat value amounts to 300 calories reaches, on the average, 22 grammes, increasing, therefore, in comparison with the fasting condition, by 70 per cent. During fever the elimination of water by the skin in man increases after partaking of food almost in the

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same degree as when the temperature is normal. In fever the organism eliminates by the lungs more water, even during fasting, than a healthy individual does after a moderate meal; the augmentation amounts to about 50 per cent. The increase is, however, only small. The whole must be regarded, as already stated, as merely a disturbance of the processes connected with the output of water upon which heat regulation depends; in this way the insufficiency of the elimination of water by the skin in fever takes part in the production of fever. The total exchange of water in fever is not thereby elucidated. It is, indeed, certain that the total amount of water evaporated often increases during the rise of temperature—of course, not to such an extent as to bring the total output of heat to the normal.

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6. The Position of Infective Fever among the different Forms of Pyrexia.

When febrile rise of temperature is considered as far as possible apart from other forms of pyrexia, a very uncertain and ill-defined territory is entered upon. In spite of the abundance of material at our disposal, it is almost impossible, from the absence of safe guidance among the labyrinth of details with which we have to deal, to fashion out of the latter a comprehensible general picture of infective fever. Of the two possible ways of investigating this pathological problem, the manner in which the causes of the syndrome in question act has been studied rather than these causes themselves.

The following constitute the most important forms of pyrexia with which comparison has to be made.

1. Pyrexia due to cerebral puncture (of the corpus striatum, according

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to Sachs and Aronsohn, and also Girard; of other parts of the brain, according to various other observers).

2. Increase of body temperature, sometimes observed in convulsions, in hysteria, in cerebral tumour, and other focal cerebral lesions.

3. The so-called reflex fever—*e.g.*, of the urethra (?)—rise of temperature following lesions of the cervical cord, or due to non-bacterial morbid conditions ("aseptic fever" following subcutaneous fractures, large hæmatomata, or laking of red blood cells), or possibly due to "fibrin ferment"; the significance of albumose is doubtful.

4. The "indirect" raising of temperature by means of salts and of compounds acting like salts (urea, amino-acids, iodine, silver, oil of mustard, turpentine).

5. Pyrexia due to poisons acting on the central nervous system (caffeine, atropine, cocaine), to tetrahydronaphthylamin, etc., and to insolation.

Of the various characters presented by infective febrile processes, only two possess a special significance. When Aronsohn and Sachs showed in 1884 that rise of temperature follows injury to the corpus callosum in rabbits, the problem of fever seemed forthwith settled and a pathogenetic turning-point obtained, round which all the individual symptoms making up the classical clinical syndrome of fever naturally grouped themselves. The existence of a heat-centre being admitted, the conclusion followed that the toxines calling forth fever exercised a chemical stimulation of that part of the central nervous system which is mechanically stimulated by puncture. Furthermore, insolation presents many points of similarity with fever.

A priori, pyrexia appears possible—

1. By interference with the central regulating apparatus in the brain, which preserves a normal exchange of heat, an appropriate production being accompanied by a corresponding output of heat.

2. By simultaneous alteration of heat-production and output in an unequal degree occurring during overproduction of heat, the central regulating apparatus, which is concerned in removing the abnormal degree of warmth, acting too sluggishly. Combinations of these two modes, as also the overproduction itself and other factors, come into play.

Now, infective fever in man exhibits some features which cannot easily be attributed to increased heat-production with normal but insufficient output, or to unchanged formation of heat, accompanied with lessened removal, or to an association of the two modes. It has been found that in fever heat-production may or may not be increased; during the onset of fever it has been found to be increased [direct calorimetric investigations on animals by Rosenthal, Hildebrandt, Krehl and Matthes, and Nebelthau; determination of gaseous exchange, metabolism and energy supply, by May on animals, by A. Loewy on man], or normal or even diminished [Senator, Krehl and Matthes, Nebelthau and Stähelin]; during the course of fever increased heat-production is met with [calorimetric observations by Hildebrandt, Nebelthau, Krehl and Matthes, and Rosenthal, estimation of metabolism and consumption of energy by Kraus, May, Stähelin, Riethus, and others], but is much more frequently wanting [Liebermeister, Rosenthal, Kraus, Nebelthau, Krehl and Matthes,

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Riethus, and others]. The output of heat was found by Nebelthau to be as a rule increased during the onset and height of fever; according to Krehl and Matthes, a diminution usually takes place during the first period, and an increase during the height of the fever. During the defervescence the heat output may still increase [Krehl and Matthes] or may diminish [Kollaps]. Of course the absolute extent of metabolism in itself affords no measure either of normal body temperature or of pyrexia, and an increase above the normal is often wanting; such an increase, indeed, presupposes in each case an absolute or relative diminution of the output of heat. All the variations just described bear the stamp of irregularity. In different stages and kinds of infective fever various anomalies are met with. These variations fail to afford an explanation of how it is that the temperature in fever often remains constant for a long time, that the temperature chart shows a cyclical course in different infective processes; that during the external application of cold heat-production is increased, the temperature reaching its high level subsequently; that after treatment with antipyretics the temperature constantly rises again; and that in fever the patient regulates his heat-supply. This regulation is adapted to extreme demands, though our knowledge in respect of smaller details is incomplete; no typical disturbance of regulation is observable. Consequently the conjecture arises of itself that the disturbances of heat-production and output already mentioned are merely means by which the organism attempts to reach a common end. Thus we are led again, in spite of the well-known objections of Wunderlich, Cohnheim, Senator, and others, to one of the fundamental tenets of Liebermeister's teaching—namely, that in fever the temperature of the organism is adjusted at a higher level. We understand in this way how the body endeavours, in spite of existing differences of heat-production and ouput, to reach, and subsequently to maintain, that higher level. Liebermeister's view has been experimentally tested, especially by Filehne and his pupils, and also by Loewit. We look upon his view as an established fact. The regulating centre may be regarded as so stimulated by the cause of the fever that it reacts to a normal external temperature as it ordinarily does to the external application of cold.

In pyrexia due to puncture of the heat-centre it has been shown by Richter, Filehne's pupil, that one character of the raised adjustment—namely, rapid compensatory regulation—is not equally well exhibited; the animals do not respond either to the application of heat or to that of cold by a complete counter-regulation—their temperature, in fact, shows a characteristic lability. In contrast to normal animals suffering from fever, rabbits after puncture do not shiver or stretch themselves out in response to appropriate changes of external temperature. The absence of this response is of course in no sense a proof of the disappearance of heat-regulative capacity, since chemical heat-regulation is demonstrable by direct and indirect calorimetric measurement before actual shivering is recognisable. Schultze also brings forward further arguments tending to show that animals possess the power of heat-regulation after cerebral puncture. All the same, it appears to us that the torpid con-

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dition which these animals exhibit constitutes the essential difference between pyrexia due to puncture and that seen in fever. For although, according to the observations at present available, heat-production due to puncture is always increased (and this is not universally so in infective fever), yet, strictly speaking, this is not all. No matter what the actual production of heat may be, adjustment of temperature to a higher level is possible, though experience shows that this takes place more readily when heat-production is increased. Augmented metabolism and energy consumption are, in rise of temperature due to puncture and also to infective processes, disturbances of function co-ordinated in the same (*cf.* Section 2), and not in opposite directions. Certain stages, perhaps also certain forms of fever in which increased oxidation is wanting, show, in fact, this relative independence; infective fever of the same intensity as that following puncture ought, moreover, to exhibit, as a rule, increased heat-production. The output is in both cases less than the production of heat, being either lowered [Gottlieb for puncture, Krehl and Matthes for infective fever], or in any case raised in a diminished degree [Schultze for puncture, Nebelthau for fever]. Regarding the mode of distribution for the total output, we are in both cases, particularly as to perspiration and infective rise of temperature, either without sufficient data, or we fail to discover any fundamental difference. Lastly, with regard to the material from which heat is produced, no qualitative difference has been shown to exist. We know now (*cf.* Section 2) that the increased consumption of protein may possess a different significance; protein does not necessarily take a considerably greater part in the absolute increase of heat-production, since at the same time the combustion of fat may be directly increased. Augmented protein destruction occurs in rise of temperature following puncture; at most quantitative differences are observable. And even when calories derived from protein preponderate markedly in infective processes, nevertheless, a close connection between febrile pyrexia and increased nitrogen metabolism could be confidently asserted only if it could be shown with certainty that during fever the stimulation of the central regulative apparatus is occasioned not only by a special and characteristic mode of protein cleavage, which has taken the place of the destruction of non-nitrogenous material, but also by definite products of this specific protein disintegration. But as long as this is impossible, we do not see that any advantage is to be gained by restricting the range of our clinical conception of fever to those affections in which both stimulation of the regulative centre and also the "special mode" of protein destruction are met with.

The case may be stated quite impartially by saying that in the general reaction to infection two parallel disturbances of function occur, and that these tend in the same direction. On the one hand, stimulation of the regulative centre, which adjusts the body temperature at a higher level (febrile pyrexia), and, on the other hand, an action upon the cells, causing augmented metabolism and consumption of energy. These two co-ordinated functional disturbances are associated not only by the cause of the fever, but also by a pathogenesis which is in part common to both, since the increased oxidation is conjectured to originate not

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directly in the tissues, but rather in the nervous system. The production of pyrexia following puncture of the brain is not, as Hirsch and Rolly believed, dependent upon the glycogen content of the organs; fasting animals, possessing only relatively a small amount of glycogen, react both to puncture and to bacterial infection by a rise of temperature, just as do animals which have been presumably made quite free from glycogen by means of strychnine injections.

We are, therefore, far from postulating a fundamental difference between the pyrexia due to puncture of the heat-centre and that occurring in infective fever. But the difference in counter-regulation in the two cases—indeed, the lability of the animals after cerebral puncture, prevent us for the present from assuming without any reservation that febrile toxines and cerebral puncture possess an identical starting-point, which is in the one case stimulated mechanically, in the other chemically. At any rate, the excitants of fever affect qualitatively similar heat-regulating centres. But in no case can the whole syndrome of fever be explained as centred in a localized functional or organic lesion. The stimulated centres constitute merely one link in the chain of varied vital functions damaged by the infective poisoning, and pyrexia following cerebral puncture is at best an experimental paradigma of such a link.

Various anomalies of heat-regulation in general may be referred to which favour the alternative assumption of a lessened sensibility (a direct morbid effect) of the regulative apparatus and a resulting relative or absolute limitation of heat-output in fever. Reference may again be made to the fact observed by Stern and Krehl that a patient during fever regulates against the application of heat and cold, also to the long-continued maintenance of high temperature in fever when only slight diurnal variations are seen, and to the typically cyclical course of many infective processes so characteristically exhibited in the temperature chart. If, on the other hand, it should appear, from determinations of total metabolism and energy consumption, that a fever patient responds to the application of external cold by increasing his calorie production less or more slowly than normal, such an event would not seriously militate against the view adopted above, which reduces regulation to adjusted liberation and discharge of a definite supply of energy. The occurrence of this depends upon the excitability of the central nervous system, which may be compared to a harp in which the key may be changed by means of a pedal. Without any change of the tune a melody is transferred from one key to another. The associated co-ordination of two thermo-regulative effects (raising of body temperature and increase of total oxidation) corresponds to the progress of the harp from the old-fashioned instrument, with a separate peg for each chord, to the modern pedalled harp. Unfortunately we have little knowledge of how the organism acts with regard to greater heat-production within itself. All we know is that in fever abundant diet does not lead to any noticeable rise of temperature, as is shown by daily experience—as, for example, in the later stages of typhoid. The so-called dynamical action of an abundant protein diet may, without prejudice to the theory of Liebermeister and Filehne, possess another significance.

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The regulation of the heat-supply in fever, as we conceive it to occur, takes place like that of a water-bath provided with a water-level tube. The second mode of occurrence of a rise of temperature (lowered sensitiveness, insufficiency of the apparatus regulating discharge of heat), on the other hand, may be compared with increased weighting of the safety-valve of a tube exposed to pressure. The fact that in fever, in spite of

CASE 1 (see p. 149).

Time.	*Manometer.*	*Thermometer.*	*Axillary Temperature.*	*Room Temperature.*	*Remarks.*
			°C.	°C.	
11.50	45·0	25·90	36·6	19·0	—
11.55	46·5	26·10	—	—	—
12	48·5	26·30	36·6	—	—
12.5	50·0	26·50	—	—	—
12.10	53·0	26·60	—	—	—
12.15	55·0	26·75	—	—	—
12.20	54·5	26·90	—	—	—
12.25	55·5	26·95	—	—	—
12.30	60·0	27·10	—	—	—
12.35	61·0	27·15	—	—	—
12.40	61·0	27·20	—	—	—
12.45	61·0	27·20	36·6	19·3	—

CASE 2.

Time.	*Manometer.*	*Thermometer.*	*Body Temperature.*	*Remarks.*
		°C.	°C.	
11.5	52·0	23·05	37·3	—
11.10	58·0	23·80	—	—
11.15	63·0	24·35	—	—
11.20	66·0	24·70	—	—
11.25	68·5	24·95	—	—
11.30	71·0	25·15	—	—
11.35	75·0	25·35	—	—
11.40	75·0	25·55	37·3	—
11.45	75·5	25·70	—	Subject began cautiously to swing about with his right arm a 5-kilogramme weight. Did not overexert himself, but tired himself a little. Face became flushed.
11.50	77·0	25·85	—	—
11.55	82·0	26·10	—	—
12	86·5	26·40	37·3	Muscular work ended. Room temperature 17·1° R. Abnormal sensation in fingers.
12.5	90·0	26·70	—	—
12.10	92·0	26·90	—	—
12.15	91·5	27·00	—	—
12.20	93·0	27·00	—	—
12.25	93·0	27·10	—	—
12.30	93·0	27·20	—	—
12.35	93·0	27·40	—	—
12.40	93·0	27·45	37·4	—

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apparently wide differences of heat-production, every natural or artificial variation of body temperature is attended by an opposing change of the components of heat-discharge—such as, *e.g.*, conduction and radiation

CASE 3.

Time.	*Manometer.*	*Thermometer.*	*Body Temperature.*	*Remarks.*
		°C.	°C.	
30	68·5	25·00	36·70	Room temperature, 16·3° R.
3.15	68·6	24·90	—	—
3.30	68·2	25·00	—	—
3.35	68·6	25·10	—	—
3.40	68·6	25·10	36·70	—
3.45	68·5	25·06	36·80	Uncovered; no feeling of coldness.
3.50	66·0	25·00	36·90	—
3.55	64·0	24·85	—	—
4	63·5	24·70	37·00	Left Leg was moistened with water. Patient complained of coldness in both feet.
4.5	60·0	24·60	37·02	—
4.10	60·4	24·50	—	The whole body was moistened. At the time of application of cold a transitory sinking of body temperature was observed. Patient felt cold, but did not shiver, nor did his teeth chatter.
4.15	60·2	—	37·18	A block of ice applied to the feet; temperature rose. Patient experienced a sense of shivering.
4.20	59·0	24·35	37·24	Patient was wiped dry, without friction, and covered with a dry sheet.
4.25	59·2	24·30	—	Patient still shivered, soon after felt warmer; skin cool.
4.30	61·5	24·20	—	—
4.35	62·6	24·20	37·10	Patient felt comfortable; skin less cool.
4.40	63·5	24·20	—	—
4.45	64·0	24·20	37·10	—
5	62·5	24·00	37·00	—

dependent upon the condition of the peripheral vessels—is easily reconcilable with the first case supposed, and exhibits the promptness of such regulation by means of vasomotor nerves. For a long time we have been engaged in making "partial" calorimetric determinations, with Rosenthal's calorimeter, on men suffering from fever, the observations extending over several hours, and being made at different periods of the illness. Opportunity of studying rapid rise of temperature was afforded by six cases of malaria. In this condition the calorie output is always lowered as compared with the state existing before the rise of temperature. The course of events in pyrexia caused by tuberculin appears to be the same. In remittent fever the discharge of heat during pyrexia is often scanty compared with the normal. In other infective processes we have often observed, during the height of the fever, an increased discharge of heat, due to marked variations of heat-production, although the body temperature remained unaltered. Our investigations were mostly directed to the artificial and natural reduction of temperature in fever. All so-called antipyretics increase heat-discharge. In the same way,

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amyl nitrite is an effective antipyretic. Quinine acts similarly, but more slowly. The increased output of heat is observable shortly after administration of the drug, before the skin becomes hot and drops of perspiration appear. The same occurs during spontaneous disappearance of fever, but is correspondingly slower and less striking. These experiments have never been published in full; we therefore give some examples below. The heat-production is not calculated in absolute units. It is sufficient for our purpose to record the temperature of the apparatus and the manometer reading.

1. J. L., male, twenty-five years of age. Strong, not fat. Tertian malaria. Free from fever during experiment. Patient lay completely quiet, in the horizontal position, with his right arm in the apparatus. Commencement of experiment 11.16 a.m. Height of barometer, 747·5 to 747·8. (See table on p. 147.)

The above is a normal experiment for comparison with the next one. The manometer reached a condition of equilibrium at the end of seventy-nine minutes.

CASE 4.

Time.	*Manometer.*	*Thermometer.*	*Body Temperature.*	*Remarks.*
		°C.	°C.	
6.45	23·0	22·10	37·10	Subjective sense of well-being; no feeling of coldness.
6.50	23·0	22·15	37·18	—
6.55	23·5	22·30	37·20	—
7	22·0	22·40	37·30	—
7.5	21·0	22·60	37·30	Feeling of coldness.
7.10	20·0	22·70	37·50	Increased feeling of coldness. Patient received another bed-cover. Breathing hurried.
7.15	19·0	22·80	37·60	Mouth feels dry. Breathing deep, hurried.
7.20	18·0	22·90	37·65	At times slight rigor.
7.25	17·0	22·90	37·70	Respiration, 60, deep; rigor.
7.30	16·0	23·00	37·70	Rigor less marked.
7.35	15·0	23·10	37·90	Wine. Rigor increased. Room temperature, 18° R.
7.40	14·5	23·10	38·50	No rigor. Subjective feeling of coldness lessened.
7.45	14·5	23·20	38·65	No rigor. Subjective feeling of coldness.
7.50	13·0	23·20	39·00	Wine.
7.55	13·0	23·30	39·10	No feeling of coldness.
8	12·5	23·40	39·25	—
8.5	13·0	23·50	39·30	—
8.10	13·0	23·50	39·40	No feeling of coldness.
8.15	12·5	23·60	39·50	—
8.20	11·5	23·60	39·50	Wine.
8.25	11·0	23·70	39·70	—
8.30	11·0	23·70	39·80	0·8 gramme antifebrin.
8.35	12·0	23·80	39·90	—
8.40	15·0	23·80	39·85	—
8.45	13·0	23·80	40·00	—
8.50	14·5	23·90	—	—

2. Healthy medical student, twenty-seven years of age. Weight, 75·9 kilogrammes. Breakfast at 8 a.m.—coffee and bread. Partly

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CASE 5.

Time.	*Manometer.*	*Thermometer.*	*Body Temperature.*	*Remarks.*
		°C.	°C.	
1	78·8	26·1	37·50	Room temperature, 17.5° R.
1.5	78·7	26·1	37·30	—
1.10	77·0	26·0	37·30	—
1.15	74·0	26·0	37·35	—
1.20	71·5	25·9	37·50	—
1.25	69·0	25·8	37·50	—
1.30	68·5	25·8	37·50	—
1.35	70·0	25·8	37·50	—
1.40	70·0	25·7	37·50	—
1.45	70·0	25·6	37·50	—
1.50	70·0	25·6	37·50	—
1.55	70·0	25·6	37·50	—
2	70·0	25·6	37·50	—
2.5	67·0	25·5	37·50	—
2.10	67·0	25·4	37·50	—
2.15	66·0	25·4	37·65	—
2.20	65·0	25·4	37·80	—
2.25	64·0	25·3	37·80	—
2.30	62·0	25·2	37·90	No rigor.
2.35	61·0	25·1	37·90	—
2.40	60·0	25·1	37·90	—
2.45	60·0	25·1	38·00	—
2.50	58·0	25·0	38·00	—
2.55	56·0	24·9	38·10	—
3	54·0	24·8	38·50	—
3.5	53·0	24·6	38·10	—
3.10	52·0	24·6	38·20	—
3.15	52·0	24·6	38·30	—
3.20	51·5	24·5	—	—
3.25	51·0	24·5	38·30	—
3.30	50·0	24·4	38·30	—
3.35	50·0	24·4	38·40	—
3.40	50·5	24·4	38·40	—
3.45	49·6	24·4	38·50	—
3.50	50·1	24·3	—	Feeling of coldness.
3.55	50·2	24·3	—	—
4	50·1	24·3	38·60	Patient complained of being cold.
4.5	51·5	24·3	—	—
4.10	48·0	24·2	38·70	No shivering.
4.15	47·3	24·1	—	—
4.20	46·8	24·1	38·80	Feeling of coldness increased.
4.25	46·0	24·1	38·90	Slight rigor. Pulse 80.
4.30	46·0	24·0	—	—
4.35	45·0	24·0	39·00	—
4.40	43·8	24·0	39·10	—
4.45	39·2	23·9	39·30	—
4.50	33·0	23·9	39·30	—
4.55	31·0	23·9	—	Feeling of coldness; slight rigor.
5	31·5	23·9	39·50	—
5.5	31·5	23·9	39·60	—
5.10	30·5	23·9	39·60	—

dressed. Left arm in calorimeter. Height of barometer, 743·5. Room temperature, 15·75 R. Commencement of experiment, 10.50 a.m.

After the lapse of forty-five minutes the manometer reading became constant. The subject then swung a 5-kilogramme weight about with his right arm for fifteen minutes. After this muscular work was ended

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his body temperature did not rise more than 0·1°. At the end of a further period of forty minutes the manometer reading became again constant at 93·0 centimetres. The experiment shows that during

CASE 6.

Time.	*Manometer.*	*Thermometer.*	*Body Temperature.*	*Remarks.*
		°C.	°C.	
8.30	44·00	21·70	38·95	Strong feeling of coldness. Rigor.
8.35	44·00	21·80	39·10	—
8.40	45·00	22·00	39·40	Rigor less.
8.45	43·00	22·20	39·75	—
8.50	44·00	22·20	40·00	—
8.55	43·00	22·30	40·10	Feeling of coldness diminished.
9	44·00	22·40	40·10	Feeling of coldness disappeared.
9.5	43·50	22·50	40·10	Rigor scarcely recognisable.
9.10	41·50	22·50	40·15	—
9.15	40·00	22·60	40·80	Patient felt neither hot nor cold. Rigor had disappeared.
9.20	41·50	22·65	40·20	Patient felt warmer.
9.25	42·00	22·70	40·30	—
9.25	40·05	22·70	40·50	0·6 gramme antifebrin.
9.40	40·00	22·80	—	—
9.45	38·00	22·80	—	—
9.50	33·00	22·90	—	—
9.55	40·00	23·10	40·30	—
10	45·00	23·50	40·25	—
10.5	53·00	24·10	40·25	—
10.10	51·50	24·30	40·25	0·4 gramme antifebrin.
10.15	52·00	24·40	—	—
10.20	58·50	24·70	40·00	—
10.25	61·00	24·90	40·00	Patient became restless, continually moving.
10.30	67·00	25·00	39·90	No perspiration.

muscular work, in consequence of the increased heat-production and unchanged body temperature, the discharge of heat correspondingly increases.

CASE 7.

Time.	*Manometer.*	*Thermometer.*	*Body Temperature.*	*Remarks.*
		°C.	°C.	
6	52·0	23·5	37·5	—
6.10	57·0	24·0	37·6	—
6.20	57·0	24·1	37·2	No shivering.
6.30	57·0	24·2	37·5	—
6.40	57·0	24·2	37·9	—
6.50	54·0	24·1	38·0	—
8	53·0	24·1	38·2	—
8.10	50·0	24·0	38·3	—
8.20	48·0	23·9	38·4	—
8.30	43·5	23·9	38·6	—
8.40	44·0	23·8	38·7	—
8.50	42·2	23·8	38·8	—
9	42·5	23·8	38·8	—

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CASE 8.

Time.	*Mano-meter.*	*Thermo-meter.*	*Body Temper-ature.*	*Remarks.*
		°C.	°C.	
12.30	**46·5**	22·70	39·75	1·5 gramme quinine per os; then some milk.
12.45	55·0	23·50	39·69	Pulse 108.
12.50	57·0	23·60	39·65	—
1	57·0	23·80	39·63	—
1.5	65·0	24·30	39·50	—
1.10	71·0	24·70	39·50	Vomiting.
1.20	80·0	25·40	39·30	Perspiration.
1.25	87·5	25·80	39·25	Breathing deep. Tinnitus aurium.
1.30	91·5	26·10	39·12	Feels unwell.
1.35	95·0	26·50	39·10	—
1.40	100·0	26·70	39·00	—
1.45	102·0	26·95	38·95	—
1.50	104·0	27·10	38·90	—
2	105·5	27·40	38·73	—
2.10	105·0	27·50	38·60	—
2.20	103·0	27·45	38·55	—
2.30	101·5	27·40	38·50	—
2.35	100·0	27·40	38·45	—

3. Healthy male, thirty-five years of age. Right arm in cylinder. Subject recumbent and covered; at 1.50 a.m., when the experiment

CASE 9.

Time.	*Mano-meter.*	*Thermo-meter.*	*Body Temper-ature.*	*Remarks.*
		°C.	°C.	
6.5	34·5	22·40	40·34	Increased feeling of warmth. Patient coughing continually.
6.10	**36·2**	22·60	—	—
6.15	**36·0**	22·70	—	Cough very troublesome.
6.20	**36·5**	22·74	40·34	0·5 gramme antifebrin.
6.25	37·0	22·81	—	Pulse 140; skin dry.
6.30	38·2	22·90	40·30	—
6.35	40·0	23·00	—	Forehead moist.
6.40	43·2	23·09	40·25	Pulse 140; skin dry.
6.45	47·5	23·30	40·10	Skin not moist.
6.50	53·2	23·60	40·10	No perspiration.
6.55	58·0	23·90	40·03	—
7	61·5	24·20	40·00	0·5 gramme antifebrin.
7.5	63·5	24·42	40·00	Skin dry.
7.10	67·4	24·62	40·00	Skin somewhat moist.
7.15	75·0	25·02	39·90	Perspiration commencing.
7.20	83·5	25·55	39·80	Perspiration moderate.
7.25	92·5	26·05	39·70	Perspiration slightly increased.
7.30	100·0	26·50	39·40	Perspiration marked.
7.35	105·0	26·90	39·30	—
7.40	108·5	27·20	—	Perspiration continues.
7.45	109·5	27·45	39·10	—
7.50	114·0	27·60	38·90	—
7.55	116·5	27·85	38·90	Feeling of warmth.
8	118·0	28·00	38·80	—
8.5	122·5	28·70	38·70	Room temperature, 17° R.

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commenced, was uncovered. Barometer, 752; room temperature, 17° R.

The above case illustrates healthy heat-regulation when cold is applied to the skin. Constant reading of the manometer at end of seventy minutes. When uncovered a slight lessening of heat-discharge occurred. Also after application of water to the body a lessening of heat-discharge occurred, attended with a sensation of cold. After the whole body had been moistened the body temperature rose 0·2 °. Although from this time onwards the patient was covered, and experienced a subjective feeling of warmth and of well-being, the rise of heat-discharge continued, and the body temperature fell from 37·24° C. to 37° C. Attention should be paid

CASE 10.

Time.	*Manometer.*	*Thermometer.*	*Body Temperature.*	*Remarks.*
		°C.	°C.	
9.25	34·9	24·60	40·00	—
9.40	35·0	24·60	39·90	1 gramme antifebrin.
9.50	35·0	24·60	39·60	No perspiration. Room temperature, 17° R.
10	38·0	24·75	39·60	—
10.10	44·0	25·10	39·40	—
10.20	51·0	25·40	39·20	—
10.30	55·0	25·70	38·80	Skin moist.
10.45	57·0	26·00	38·50	—
11	57·0	26·15	38·20	—
11.15	57·5	26·30	38·00	Patient perspired very little. Forehead dry.
11.30	56·0	26·25	37·70	—
12	55·0	26·10	37·35	—
12.30	54·0	26·10	37·10	—
12.45	52·7	25·90	36·85	—

to the simultaneous compensatory alteration of heat-discharge and of body temperature.

4. Malaria. Fasting since 6 p.m. on the preceding day. Room temperature, 16·5° R. Commencement of experiment, 5.14 a.m.

This experiment illustrates the above-described course of events during the onset of fever. (See table on p. 149.)

5. A. S., malaria. Partook of coffee at an early hour; at 9.30 a.m. half a glass of milk and one egg. Experiment commenced at 11.33 a.m., when the room temperature was 16·5° R.

The above experiment extended over five hours. The discharge of heat slowly diminished, while the body temperature increased. The augmented production of heat in the interior of the body began a long time before a subjective feeling of cold made its appearance. The discharge of heat sank to a low figure. (See table on p. 150.)

6. Malaria. Fasting since yesterday. Height of barometer, 743. Room temperature, 17.7° R. Commencement of experiment, 7.48 a.m.

The experiment was discontinued because of patient's discomfort. The reaction at the height of the attack is exhibited, also the effect of antifebrin. (See table on p. 151.)

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7. 0·015-gramme tuberculin injected at 12.30 p.m. Temperature at commencement of experiment (5.13 p.m.), 36·5° C. Room temperature, 17° R. (See table on p. 151.)

CASE 11.

Time.	*Manometer.*	*Thermometer.*	*Body Temperature.*	*Remarks.*
		°C.	°C.	
5.45	15·5	26·45	40·00	—
5.50	15·0	26·50	—	—
5.55	16·5	27·05	40·04	Patient drank some water.
6	17·5	27·20	40·10	Pulse 128. One gramme antifebrin.
6.5	20·0	27·50	—	Skin dry and warm. Drank some water.
6.10	21·5	27·70	—	Skin very moist.
6.15	24·5	28·25	39·90	Sweat visible, but not in drops.
6.20	26·7	28·90	39·80	—
6.25	29·5	29·40	39·60	Perspiration increased.
6.30	31·0	29·75	39·40	—
6.35	32·0	30·10	—	Pulse 140.
6.40	32·8	30·30	39·10	—
6.45	33·5	30·40	—	—
6.50	33·8	30·50	38·80	—
6.55	34·0	30·63	—	—
7	34·8	30·70	38·80	—
7.5	34·0	30·60	—	—
7.10	31·8	30·60	38·60	Pulse 126.
7.15	31·0	30·60	38·60	—

The experiment illustrates a slow onset of fever.

8. J. N., thirty years of age. Pneumonia. 11 a.m., 1·5 grammes quinine by the mouth. Left arm in apparatus. Room temperature, 16·5°. Commencement of experiment, 11.3 a.m.

CASE 12.

Time.	*Manometer.*	*Thermometer.*	*Body Temperature.*	*Remarks.*
		°C.	°C.	
6	78·2	26·06	39·30	Patient coughed a little.
6.5	79·0	26·20	—	—
6.10	79·9	26·35	—	—
6.15	81·5	26·56	—	Slight cough.
6.20	81·5	26·59	—	0·5 grammes antifebrin.
6.25	82·5	26·80	—	—
6.30	86·5	27·00	39·00	No sweating.
6.35	95·5	27·25	—	Some cough; sweating commencing.
6.40	101·5	27·70	—	Sweating increased.
6.45	106·5	28·00	38·50	Some cough; sweating further increased.
6.50	109·5	28·20	—	—
6.55	113·0	28·37	—	Room temperature, 17·3° R.
7	114·0	28·50	—	—
7.5	115·0	28·60	37·95	Abundant perspiration. Subjective sense of well-being.

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CASE 13.

Time.	*Mano-meter.*	*Thermo-meter.*	*Body Temper-ature.*	*Remarks.*
		°C	°C.	
5.45	80·0	25·35	39·30	—
5.50	82·5	26·70	—	—
5.55	85·0	26·95	—	—
6	86·5	27·20	—	—
6.5	89·0	27·40	39·30	0·5 gramme antifebrin.
6.10	98·5	27·80	—	—
6.15	104·5	28·30	—	—
6.20	111·5	28·70	—	Room temperature, 17·4° R.
6.25	118·5	29·10	38·90	Somewhat marked sweating.
6.30	122·5	29·40	—	—
6.35	126·0	29·60	—	—
6.40	129·0	29·85	—	—
6.45	131·0	30·00	38·40	—
6.50	122·0	30·10	—	—
6.55	133·0	30·15	—	—
7	133·5	30·20	—	—
7.5	133·5	30·29	—	Marked sweating.
7.10	133·0	30·30	37·90	—

The experiment illustrates a slow fall of temperature under the influence of quinine. (See table on p. 152.)

9. Girl, twelve years of age, suffering from phthisis. Tuberculin 0·01 injected at midday, when the temperature had already commenced a

CASE 14.

Time.	*Mano-meter.*	*Thermo-meter.*	*Body Temper-ature.*	*Remarks.*
		°C.	°C.	
10.45	77·5	22·60	39·50	Patient restless and complaining; skin dry; sips a little water.
10.50	80·5	22·70	—	—
10.55	83·0	22·80	39·60	—
11	86·5	22·90	—	—
11.5	89·5	23·00	—	—
11.10	90·0	23·20	—	—
11.15	90·5	23·25	—	—
11.20	95·0	23·30	—	Skin somewhat moist.
11.25	101·0	23·45	—	Perspiration commenced.
11.30	107·5	23·70	—	Perspiration increasing.
11.35	114·9	23·90	—	Drops of perspiration visible.
11.40	122·5	24·20	—	Further increase of perspiration.
11.45	130·5	24·50	38·90	—
11.50	136·0	24·80	—	Room temperature, 16·2° R.
11.55	140·0	25·00	—	—
12	145·0	25·30	38·30	Perspiration marked.
12.5	149·5	25·45	—	—
12.10	153·0	25·60	—	Perspiration less.
12.15	155·0	25·75	—	—
12.20	156·5	25·80	38·00	—
12.25	157·5	25·85	—	Perspiration slight.
12.30	157·0	25·80	37·80	Pulse 104.

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CASE 15.

Time.	*Manometer.*	*Thermometer.*	*Body Temperature.*	*Remarks.*
		°C.	°C.	
12	48·0	23·65	38·60	Patient half dozing.
12.5	48·5	23·79	—	—
12.10	50·0	23·85	38·55	—
12.15	51·5	23·90	—	—
12.20	52·5	24·00	—	—
12.25	53·0	24·05	—	—
12.30	54·3	24·10	—	—
12.35	54·4	24·12	—	—
12.40	62·5	24·40	—	—
12.45	69·0	24·70	38·30	Pulse 90. Skin dry. Fine droplets of perspiration on face.
12.50	75·5	25·00	—	—
12.55	79·5	25·20	—	Perspiration more marked.
1	85·0	25·40	37·80	Perspiration very marked.
1.5	88·5	25·60	—	—
1.10	91·0	25·70	—	Patient more lively.
1.15	93·5	25·80	—	Face covered with perspiration. Feeling better.
1.20	95·0	25·90	—	—
1.25	96·5	25·91	—	Room temperature, 16·5°.
1.30	97·0	25·94	37·40	Skin warm. Cognac administered.

rapid rise (from 38° C. to 40° C.), attended with shivering and slight cough. Temperature before injection, 37·8° C.; slight shivering during this time. At 5.20 p.m. marked rigor. At 5.25 p.m. slight rigor, much coughing. 5.40 p.m., slight feeling of warmth. Room temperature, 16·5°. Experiment commenced at 5.20 p.m. (See table on p. 152.)

The above illustrates fall of temperature after antifebrin.

10. M., typhoid (diabetes insipidus). Patient does not perspire. Left arm in cylinder. Barometer, 748·5. Room temperature, 17°. Commencement of experiment, 8.45 a.m. (See table on p. 153.)

Fall of temperature after antifebrin.

11. Girl, twenty-two years of age. Abortive scarlatina. Rash appeared on October 28 to 29. Experiment made on October 31, commencing at 5.10 p.m. Left arm placed in apparatus. Room temperature, 18·2°. (See table on p. 154.)

12. J. R. Typhoid. At midday soup and an egg; no food since. Left arm in apparatus. Barometer, 742·2. Room temperature, 17·0°. Experiment commenced at 5.2 p.m. 0·5 gramme antifebrin. (See table on p. 154.)

13. J. S. Typhoid. At midday received soup and an egg. Left arm in apparatus. Patient recumbent in bed. Barometer, 743·5. Room temperature, 17·5°. Experiment commenced at 5.8 p.m. (See table on p. 155.)

14. A. G. Typhoid. At 6 a.m. a glass of milk; no nourishment subsequently. Barometer, 749·0. Room temperature, 15·8° R. Experiment commenced at 9.42 a.m. Two grammes antipyrin. (See table on p. 155.)

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15. Typhoid. Left arm in apparatus. Barometer, 746·8. Room temperature, 16·2° R. Temperature in axilla before commencement of experiment, 38·4°. Commencement of experiment at 9 a.m. Two grammes antipyrin. (See table on p. 156.)

CASE 16.

Time.	*Manometer.*	*Thermometer.*	*Body Temperature.*	*Remarks.*
		°C.	°C.	
5.40	111·0	24·90	39·30	—
5.45	113·2	25·05	39·00	Pulse 120; somewhat irregular, full; exhibits respiratory variations; at times intermittent.
5.50	116·2	25·10	—	—
5.55	119·1	25·20	—	—
6	121·5	25·45	—	—
6.5	124·0	25·51	—	—
6.10	127·0	25·61	—	—
6.15	129·0	25·70	—	—
6.20	130·6	25·80	39·04	Pulse 108.
6.25	131·7	25·86	—	—
6.30	131·5	25·90	—	Amyl nitrite administered cautiously. Pulse 102, at times intermittent.
6.35	134·5	25·90	—	Pulse 120. Face red, previously pale.
6.40	135·8	26·00	—	Pulse 116. Perspiration commencing.
6.45	148·0	26·20	—	Pulse 136. Skin moist; beads of perspiration on the face.
6.50	157·5	26·65	—	—
6.55	164·0	27·06	—	Room temperature, 15·8°. Pulse 116.
7	167·2	27·20	38·67	Marked perspiration.

The above experiment illustrates the action of antipyrin in fever. The same effect is produced as with antifebrin.

16. L. Typhoid. Patient fasting all day, except for three spoonfuls of soup at midday. Barometer, 749. Room temperature, 15·3°. Experiment commenced 4.52 p.m. (See above, action of amyl nitrite.)

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7. The Production of Acetone Bodies and of Acid in Febrile Conditions.

The first communications upon febrile acetonuria and diaceturia were made by von Jaksch. All three acetone bodies—namely, acetone itself, aceto-acetic acid, and β-oxybutyric acid—have now been found in the urine of patients with elevated temperature. According to von Jaksch, aceto-acetic acid was seldom found in febrile conditions affecting adults, and was of grave import. Such a prognosis is not, however, in reality attached to aceto-acetic acid, which is very commonly found in the urine of children, not only during the eruptive stage of exanthemata and constantly during high-continued fever [Schrack], but also in slight intestinal affections. Von Jaksch supposed that in diaceturia the acetone originally present entered into combination (with formic and other acids), so that no more preformed acetone appeared in the urine. Since the associated appearance of β-oxybutyric acid has become known no one doubts that β-oxybutyric acid, in accordance with the general course of metabolism, forms the precursor of aceto-acetic acid and of acetone. It is thus easily understood how, in a certain class of cases, β-oxybutyric acid is completely oxidized to acetone, while in other cases, in consequence of more severe disturbance of metabolism, oxidation does not proceed beyond β-oxybutyric acid. Acetone appears first, then aceto-acetic acid, and finally β-oxybutyric acid, and they disappear in the reverse order. β-oxybutyric acid was first found in scarlatina and measles by E. Külz, and by von Noorden in typhoid and severe dysentery. The presence of this acid, moreover, is, as a rule, not of bad prognostic import; its appearance indicates a more strongly-marked, but at the same time limited, disturbance of oxidation in a special direction.

The extent to which acetone bodies are formed in fever is much less than in diabetes, and, indeed, less than in complete inanition. Quantitatively the amount of acetone reaches 500 milligrammes [von Jaksch] and 400 milligrammes [Hirschfeld]. Inasmuch as acetone is found, in addition to the urine, in respired air, blood, sweat, gastric juice, and in organs, accurate observations by modern methods are much to be desired. Only by simultaneous examination of total metabolism can the points of difference be recognised which, after exclusion of inanition, may be attributed either to the idiosyncrasy of the infection, or to the severity of the general reaction.

At present it is scarcely possible to decide if this or that cause is effective in producing acetone bodies in the organism during fever. It is generally admitted that continued high fever acts differently from remittent or intermittent fever, and again, that the fever of chronic diseases is different from that of acute diseases. Nevertheless, these differences may be determined by very varied factors. As yet conflicting views are held respecting the frequency with which acetone bodies are met with in various febrile affections, or the constancy with which they occur in any individual febrile state. It does not, of course, necessarily follow that acetonuria, even if directly due to toxic influences, should rise and fall

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parallel with the temperature. Von Jaksch believed that the degree of febrile acetonuria corresponded to the elevation of temperature, but we know now that he overrated the influence of pyrexia. High-continued fever may be met with in which no acetonuria occurs, and diaceturia may appear in severe or in slight affections in the absence of any rise of temperature. Von Engle was of opinion that the seat of the affection and the individuality of the patient, together with the nature of the process leading to fever, had a larger share in determining the elimination of acetone than the degree of fever. We have no doubt that the localization of the affection in the alimentary tract is of paramount importance. Botazzi and Orefici, as also Waldvogel, have emphasized the effect of individual idiosyncrasy. Furthermore, the occurrence of acetonuria during starvation has thrown doubt upon the view that febrile acetonuria is a specific toxic result of fever. Von Noorden expressed the opinion that insufficient nourishment was the cause of the acetonuria. Hirschfeld attributed acetonuria in febrile states to defect of carbohydrate in the food taken, and, as a matter of fact, febrile diaceturia and acetonuria are often observed to diminish after the administration of carbohydrates, as is also to be noted in acetonuria attending starvation or a diet of animal fat. Nevertheless, many cases are met with in which carbohydrates do not act at all readily. Botazzi and Orefici assert that the administration of sugar has little effect on febrile acetonuria, and the same has been observed by Mohr. To conclude, from these negative results, that in fever carbohydrates are not turned to account appears scarcely justified. Such cases support the view that acetonuria in fever is called forth by two factors due to the infective process—namely, inanition and fat destruction. Waldvogel's experiments on acetonuria in narcosis, in which no reduction of the amount of food taken and no dyspeptic symptoms occurred, show the possibility of acetonuria being of toxic origin. Botazzi and Orefici have, moreover, supported the view that the toxines of infective processes influence the occurrence of acetone bodies. These authors made observations on five cases of diphtheria in children—one being convalescent—in which serum was injected. The curve of acetone excretion showed a sudden fall after administration of the serum, and a second smaller fall lasting during convalescence. Blumenthal believed that some forms of infection have a special influence in inducing acetonuria and diaceturia, and referred in this connection to the action of streptococci. In diabetes an increased formation of acetone bodies occurs during febrile conditions, aceto-acetic acid and β-oxybutyric acid speedily making their appearance. Exceptions are, however, frequent.

The striking fact, observed by Regnard and Geppert, that the amount of carbonic acid in venous blood is considerably diminished in fever, was attributed to increased formation of acid in the organs, or, as Mayer first expressed it, to diminished alkalinity of the blood. This small CO_2 content of the blood was not attributed to increased aeration of the blood, because the increased depth of breathing appeared quite inconsiderable. That in the metabolism of fever the amount of fixed alkali available was small compared to the amount of acid formed seemed probable from the

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increased elimination of ammonia [Naunyn]. Koppe had already found that the daily elimination of ammonia was increased in typhoid, and Hallervorden observed the same in many other febrile conditions. Meyer was unable to find lactic acid, which was the acid first under consideration, in the blood of dogs suffering from septicæmia. Minkowski showed that the CO_2 content of arterial blood was also regularly diminished in fever, and attributed this likewise to acid-poisoning, bringing forward new arguments in support of this view. In human venous blood during fever I have demonstrated a considerable diminution of CO_2 content—namely, from 31·34 to 33·43 per cent. (by volume, pressure 76 centimetres) to 9·84 to 20·34 per cent. This occurred quite independently of the character of the infective process at work. In diabetic coma (thirteen observations) we found a minimum amount of 9·83 per cent. This diminution of CO_2 content in fever set in with a varying degree of rapidity after inoculation, and presented a certain parallelism to the severity of the symptoms. On cessation of the fever the return to normal did not at once appear.

Apart from a comparison of the clinical picture with that of poisoning by mineral acids [F. Walter], we rely, in diagnosing the presence of acid intoxication and in judging its degree, upon the direct demonstration of excessive production of certain acids in the body, and upon indirect proof of the same (the increased excretion of ammonia is in itself no longer considered to be quite free from objection when brought forward as affording such proof). According to the valuable researches upon acid production in diabetes mellitus by the Naunyn school, the presence in excess of certain combinations, not acid in themselves—such, for example, as combinations with acetone—affords presumption of the presence of acid production. Acetonuria has consequently no independent pathological position, but is merely a mild form of acid-poisoning. The quantitative estimation of the ash of the blood, or the determination of the relation of acids to fixed bases in the excreta, form a direct measure of the intensity of acid formation when attention is concentrated upon the reduction of alkali. Merely determining the degree of acidity of the urine has, according to our experience, little value. More is afforded by the lateness of the appearance of alkalinity after the administration of salts of the alkali metals by the mouth. Respecting the extent to which combinations with alkalis occur, information is afforded by determining the amount of alkaline salts in the body juices, and the increased CO_2 content of the urine due to the increased CO_2 tension in the blood, the latter being occasioned by the diminished alkalinity of the blood.

The reaction of the blood is now capable of exact definition, and was first investigated by Höber by means of gas cells, such work having been rendered possible by the precise measurements of dissociation of solutions recently determined. Fraenkel, at our suggestion, has carried out investigations upon acid production in the organism. By means of a special procedure he has found that the diminution of carbonic acid, caused by poisoning with mineral acids, and that present in diabetic coma in man, correspond to a well-defined decrease of the alkalinity of the blood minus carbonic acid. In spite of the low CO_2 content, the same was not, however, found in the blood in apnœa and fever.

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It is, of course, not to be expected that the clinical picture of acid intoxication should be always equally intense. Such a condition—when of moderate or slight intensity—may be recognisable only by very delicate methods, or may be completely overshadowed. Since the lowering of CO_2 in the blood in fever is comparable to that occurring in diabetic coma, we are no longer able to believe that the former condition is solely attributable to acid production. Naunyn has already suggested that this change in the composition of the blood is due in part, at least, to the accompanying elevation of temperature. Such a possibility cannot be neglected, in view of the observations of Mathieu and Urbain, of Geppert and of Minkowski, which agree in showing that in pyrexia due to external application of heat the CO_2 content of the blood is diminished. Possibly this decrease is an effect of the increase in frequency of respiration. During apnœa the amount of carbonic acid in the blood has been shown by Ewald and Hering to be diminished; our own observations confirm this.

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8. The Diazo-reaction.

In most febrile affections nitrogenous substances appear in the urine which give Ehrlich's so-called diazo reaction—that is to say, on the addition of sulphanilic acid, sodium nitrite and ammonia to the urine an orange-red to cherry-red coloration appears.

The nature of this reaction is still unknown. According to Ehrlich, phenols and amines give, with diazo-bodies, this colour reaction. Dolgow

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believes that compound sulpho-acids, and Clemens that hydroxyl compounds of the fatty series, take part in the reaction. Brieger and Ott were unable to arrive at any definite solution of the problem. According to Geissler and Saliew, the substances produced in the diazo reaction are formed from broken-down leucocytes, and Geissler believes that they are formed in the kidneys. Recently Clemens claims to have isolated the substance in question. From the basic lead precipitate of the urine he prepared, by means of $H_2SO_4 + BaCO_3$, the barium salts of the organic acids of the urine. The substance in question is present in that part of this fraction which is insoluble in alcohol, and being now freed from inorganic acids, urea and uric acid can be freed from purin bodies by treatment with ammoniacal silver solution. It forms a yellowish powder, precipitable by nitrate of mercury and by phosphomolybdic acid, and contains 4·2 to 5·4 per cent. nitrogen and 0·5 to 1·4 per cent. sodium. It has been already shown by Clemens that it is soluble in water and alcohol; in acid solution it may be heated without change; in ammoniacal solution it is easily decomposed. Various drugs cause the urine to give a reaction which simulates the diazo reaction. Such are opium and chrysarobin [Krokiewicz], naphthalin [Burghart], and morphia [Carcano]. Many substances, such as tannic acid [Burghart], taken in small quantities, hinder the reaction, apparently by affecting the reagents employed.

No consensus of opinion respecting the conditions under which the reaction occurs and its diagnostic and prognostic significance has yet been reached. Subsequent investigations have not added much to Ehrlich's first communication. The reaction is only exceptionally met with in afebrile chronic affections. Febrile diseases may be divided into three groups, according as the diazo reaction—

1. Is almost always absent. This is the case in articular rheumatism, meningitis, rubeola, and varicella (Nissen).

2. Is frequently present, as in severe cases of pneumonia, scarlatina, diphtheria, and erysipelas.

3. Is constantly present—namely, in typhoid, typhus, advanced phthisis, and measles.

Goldschmidt failed to obtain the reaction in influenza; Brewing repeatedly obtained it in puerperal fever and in deep-seated abscesses, and Pelzl in septicæmia. Hellendall always obtained a positive reaction in acute osteomyelitis and actinomycosis. In tuberculous joint disease the appearance of the reaction corresponds to the severity of the affection.

The diazo reaction is met with in pneumonia more frequently than was formerly imagined to be the case; Clemens obtained it in 39 out of 221 cases. In scarlatina Clemens obtained the reaction in 30 out of 87 cases, often on the second or third day of the exanthem. Scarlatina differs in this respect from measles.

In uncomplicated cases of diphtheria the reaction appears to be almost always absent. Lobligevis obtained the reaction in 1 out of 118 cases, otherwise the reaction was invariably due to scarlatina.

In measles the reaction is always present. It appears at the same time as the rash, seldom before, persists during the period of fever, and disappears with cessation of fever, at the latest six days after the crisis.

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9. Chlorides and Phosphates in Febrile Conditions.

In a large number of infective processes, particularly in pneumonia, but also in typhoid, typhus, intermittent fever, measles, and scarlatina, a retention of chlorine in the organism is met with. During convalescence the reverse takes place. Redtenbacher was the first to call attention to these facts. Retention of chlorine is not, however, observed in all infective processes, a markedly increased excretion of chlorine taking place, for example, during an attack of malaria.

Different views have been held respecting the cause of retention of chlorine in fever. Terray's assumption that the cause is to be found in retention of water has already been shown to be insufficient. Röhmann suggested that organ protein which was poor in chlorides became converted in the circulating fluid into protein rich in chlorine. Von Limbeck, Schwarz, and Hijmans van den Bergh regard the elimination of chlorine as inversely proportional to that of phosphoric acid, and believe that a retention of chlorine occurs only when the osmotic equilibrium of the body juices has been disturbed in consequence of increased P_2O_5 elimina-

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tion ; retention of chlorine thus preserves the isotony of the blood. But the elimination of phosphoric acid, which, as can readily be understood, is determined by a complicated series of factors, appears to vary much more than that of chlorine in different infective processes.

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10. Effect of Febrile Processes on the Alimentary Tract and upon the Secretion of Bile.

(*a*) *Saliva.*

The digestive secretions are lessened in fever. Decrease in salivary excretion leads to the tendency to dryness of the mouth and throat, attended with increased thirst. Among qualitative changes, alteration of the alkaline reaction of the salivary secretion (especially from the parotid) to acid has often been asserted. Jawein found that ptyalin was markedly diminished in severe febrile affections.

(*b*) *Functions of the Stomach.*

The gastric functions are, as a rule, affected in febrile diseases. Manassein's experiments show that in animals the secretion of HCl is diminished in fever. In man during acute febrile conditions the same is usually observed [Hildebrandt, G. Klemperer, O. Brieger, Schetty, Glucinzki, and others]. Complete arrest of the secretion of HCl does not occur, but the amount of HCl is so small that the affinity of the food for the acid is not satisfied. As a consequence no superfluous HCl, recognisable by anilin dyes or other means, is met with, but organic acids contained in the food, or derived from it by fermentation, preponderate in the chyme. Von Noorden obtained, together with numerous negative results, distinct evidence of HCl during high fever (acute phthisis, pneumonia, erysipelas, and scarlatina), provided that much pepper and salt were added to the meat taken. From this it follows that the torpor of the secretory organs in febrile states can be overcome by means of strong stimulation. In accord with the observations of other investigators, von Noorden always found a sufficient amount of pepsin in the chyme during febrile conditions.

In fever occurring in chronic diseases (tuberculosis), Hildebrandt, Klemperer, Schetty, and O. Brieger found the HCl secretion to be much less influenced or quite normal. After a time the secretory apparatus appears to accustom itself to the febrile state and to resume its functions.

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It must, however, be observed that the individual experiments on chronic febrile conditions showed great differences. Individual conditions of experiment may exercise great influence on the results obtained. The general nutritional state is of prime importance; should it be greatly lowered by chronic disease, a diminution of the secretion of HCl would of necessity result.

Other gastric functions are also affected. Sticker and Zweifel showed that the capacity of the mucous membrane for absorbing potassium iodide was lowered. Sticker found this to be the case during commencing or increasing febrile disturbance, less so during the disappearance of the same. These time relations appear to be of greater importance than the actual height of temperature attained.

On the other hand, the motor functions of the stomach are but little altered. Von Noorden has in a number of experiments on acute and chronic febrile conditions almost always found the stomach empty one and a quarter hours after a light meal (bread and tea). Immermann had previously shown the same to be true in febrile phthisis attended with dyspeptic disturbance.

Absorption is unaltered, for that which is not digested in the stomach is dealt with and assimilated in the intestines.

In another respect, however, disturbances of the gastric functions have a considerable influence upon metabolism in febrile states. The dyspepsia of fever is, like focal diseases of the stomach, attended with considerable loss of appetite, the patient taking small quantities of food and chiefly requiring liquids containing little solid material. The consumption of energy usually remains at least at a normal level, but the diet taken is insufficient for its requirements; this is particularly the case when the temperature is high and mental obscuration is present. The nourishment given to a patient suffering from typhoid, pneumonia, erysipelas, scarlatina, septicæmia, etc., when fever is unbroken and scarcely any desire for food manifested, represents about one-third, or, if abundance of milk is given, perhaps two-thirds, rarely more, of the material which is actually broken down. The patient oxidises his own body substance. In chronic febrile conditions the amount of food taken is very variable; for some time previously too little food has been taken, and considerable emaciation has resulted. The food taken may often be sufficient for the requirements of the poor nutritional state which has been developed, but it may not suffice for the purpose of amelioration, and frequently falls below what is necessary.

(c) *Peristalsis, Intestinal Secretion, and Formation of Bile.*

The motor functions subserving digestion are usually depressed in febrile states, so that constipation and flatulence are common. Defective peristalsis affects especially the distal part of the intestinal tract, and is not known to affect the upper end of the small intestine. Its causation is to be found partly in the patient's lying at rest in bed in the recumbent posture, and perhaps also in poverty of intestinal secretion. This condition is not, perhaps, of any importance, but it may be that, in conse-

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quence of a sense of fullness or other unpleasant sensations dependent on defective emptying of the intestines, the amount of food taken becomes less than would otherwise be the case.

In other cases diarrhœa results, becoming, however, in most infective diseases only exceptionally of serious import. Diarrhœa is well known to be the rule in typhoid, to be common in septicæmia and measles, and to be much less often encountered in other acute diseases.

Among the glands of the intestinal tract the liver occupies the first rank, and is affected in almost every acute febrile disease. Post-mortem degenerative changes in the liver cells are met with, sometimes inconsiderable, sometimes marked, varying according to the duration and nature of the illness, and largely independent of the intensity of the febrile rise of temperature.

Bidder and Schmidt found the secretion of bile to be lowered during a rigor occurring in the dog. Pisenti found in septic fever, lasting one to two days, a diminution in the secretion of bile from a fistula, the total solids being also low; the bile was in consequence more viscid, contained much mucus, and was much less darkly stained than normal.

It is well known that in infective febrile states red blood cells are destroyed in larger numbers than is normally the case, the hæmoglobin thus set free being taken up in the liver and converted into biliverdin. Experimental investigations on hæmoglobinæmia show that the bile possesses a peculiar viscidity. This assertion has, however, been questioned [E. Pick]. It is very probable that in Pisenti's experiments also destruction of hæmoglobin was the cause of the deep colour of the bile during fever. Unfortunately Pisenti did not determine the amount of biliverdin present, but merely weighed the dried residue left on evaporating the bile, from which the colouring matter cannot be calculated. Consequently no data respecting the absolute amount of biliary colouring matter eliminated in fever are available, and the conclusion that bile pigment, unlike total water and salts, is increased, rests solely upon practical experience of the increased elimination of the derived pigments, such as the hydrobilirubins, in febrile conditions.

The viscid condition of the bile in febrile conditions, in conjunction with cloudy swelling of the liver cells, due to toxic substances circulating in the blood, has apparently led to the idea that in some cases of acute infective diseases the escape of bile is hindered and icterus results. Such icterus is perhaps due to stasis of the bile, the passage into the blood and tissues of bile pigment found by the destruction of hæmoglobin being facilitated by viscidity and chemical change (coagulability) of the bile and narrowing of bile capillaries, due to cloudy swelling of the liver cells.

This stasis of bile in the smallest biliary passages is scarcely ever complete, and does not proceed far enough for the fæces to become clay-coloured and digestion of fat to be interfered with.

(*d*) *Assimilation of Food.*

An approximate idea of the degree to which the functions of the alimentary tract are carried out during febrile conditions can be obtained

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only by comparing the diet and the fæces. The unfavourable influence of pyrexia upon absorption was held to be very marked until von Hösslin showed that even in typhoid, in which pronounced fever is attended with lesions of a portion of the intestinal tract, the water, protein, and fat contained in the food taken are on the whole dealt with in much the same way as in health. Only when profuse diarrhœa occurs, which is indeed unusual in typhoid, does absorption become definitely affected, and then only as the result of the diarrhœa and the local intestinal lesions, not of the pyrexia. This is shown by Tschernoff's experiments on the fate of milk-fat in typhoid. These show that 7 to 12 per cent. passes unchanged into the fæces—that is to say, scarcely more than is the case in health—when a milk diet is taken. In some cases Tschernoff found that absorption was less well carried out immediately after recovery from typhoid than during the height of the disease. In other fevers (relapsing fever, typhus) a great loss of fat occurred, averaging 7·2 per cent. more than in health. Uffelmann also found a moderate diminution of fat absorption in children suffering from febrile affections. Sassetzky investigated the loss of nitrogen derived from milk in typhus. During health he found 3·9 to 8·1 per cent.; in fever, 7·8 to 24·4 per cent.

In this connection some observations made by von Noorden may be referred to. A patient suffering from croupous pneumonia received in the course of two days, in milk, beef-tea, eggs, biscuit, butter, and meat, 10·2 grammes nitrogen and 70 grammes fat per diem, and lost in the fæces 0·9 gramme nitrogen and 6 grammes fat per diem. These figures are normal.

A patient with tuberculosis received per diem, in bread, milk, butter, and meat, 11·6 grammes nitrogen and 85 grammes fat. The fæces contained during an afebrile period 1·0 gramme nitrogen and 6·0 grammes fat; during a sharp rise of temperature, due to tuberculin, the fæces contained 0·98 gramme nitrogen and 6·2 grammes fat.

The net result of the above investigations is that the influence of fever on absorption of food is inconsiderable. This is an important practical point to which von Hösslin attached great weight, insisting that fever should not be held to contra-indicate the administration of food whenever possible in amount necessary to maintain the patient's strength.

Nearly all the *Literature* is to be found in the first edition of this work.

11. Convalescence.

It has long been known that convalescents, like those who have been subjected for a long period of time to insufficient food, can be made to increase in weight more readily than well-nourished persons. F. Müller has observed that an addition of protein can occur in wasted and enfeebled patients on a diet which in normally nourished individuals would be insufficient to permit a nitrogenous equilibrium being attained. This observer showed that especially during convalescence from severe diseases considerable amounts of protein derived from the food were daily retained in the organism, and employed in building up again the damaged tissues.

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Svenson next attempted to determine more precisely the manner in which the building up of body substance was effected, whether exclusively by administration of food, or in addition by an accompanying diminution of oxidative processes. To this end he determined, during convalescence from typhoid and pneumonia, the respiratory exchange and protein metabolism, both during bodily rest and when fasting, and also when food was being taken and during muscular work. Svenson divided convalescence into several periods, which are especially marked in typhoid fever. In the early period, which is of short duration, the gaseous exchange is diminished, next an increase occurs in which a slight excess above the normal is met with, followed finally by a return to the normal amount. A similar variation of the respiratory quotient is met with; this is at first low, then increases to unity, and finally falls to the normal amount. A marked tendency to take up nitrogen is sometimes not observed at the beginning of convalescence, being concealed by epicritical elimination of urea, absorption of exudate, etc. The influence, under these circumstances, of diet and muscular activity upon the gaseous exchange is noteworthy. The increase of the latter due to diet is considerably greater than occurs in the same individuals subsequently to convalescence, amounting at the commencement of convalescence to 40 to 70 per cent. of the ratio observed during fasting, as against 10 to 40 per cent. subsequently to convalescence. Muscular work also increases metabolism much more than is normally the case. Benedict and Surányi have confirmed Svenson's results. A diminution of oxidative processes has, therefore, not been observed.

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CHAPTER IV

DISEASES OF THE STOMACH AND INTESTINES

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I.—DISEASES OF THE STOMACH.

Introduction.

The part played by the stomach in digestion, and therefore in metabolism, is very important, corresponding to its many different functions. To summarize the latter briefly, they consist in the temporary storage of the ingesta, their transformation into a condition suitable for intestinal digestion, and their gradual propulsion into the bowel. Compared to these chemical and motor processes, the absorptive power of the stomach is of minor importance. Practically no water is taken up by it, and of substances in solution other than alcohol little more than traces of sugar, dextrin, albumoses, and salts are absorbed.

It is only of recent years that we have understood what the proper preparation of the food for intestinal digestion means. It consists in: (1) Bringing the ingesta to the proper temperature; (2) diluting irritant, and especially too concentrated, solutions (*Verdünnungssekretion* of von Mering); (3) disinfection by constant churning of the food in the hydrochloric acid; (4) breaking the larger pieces into particles; (5) by the action of ferments converting part of the food into a state ready for absorption. As Moritz (1) has well said, the stomach is the guardian of the more delicate intestine, and hands on to the duodenum only those portions of the ingesta which have been properly prepared.

The disintegration of the food in the stomach is more chemical than mechanical. The gastric juice rapidly dissolves connective tissues, as Schmidt (2, 3) has shown for meat and H. Strauss (4) for bread. This is an important function, which—at all events, for meat—is not performed by the juices of the intestine.

In regard to the action of ferments in dissolving food in the stomach, the works of Pawlow (5), Müller (6), Hensay (7), Dauber (8), Schüle (9), Heinrich (10), Moritz (1), and others are available. Normally 30 to 40 per cent. of chopped meat is thus dissolved, 20 to 60 per cent. of plasmon [Rosenberg], 60 to 80 per cent. of boiled starch (salivary action). According to Volhard (11), as much as 60 per cent. of emulsified fat is

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converted into free fatty acids by a fat-splitting ferment discovered by him in the stomach.[1]

In digestive disturbances the individual functions of the stomach are concerned, each in varying degree. Although a single function is seldom affected by itself, it is possible from the clinical standpoint to distinguish cases of diseased secretion from those of diseased motility. Cases in which there are fermentative processes of bacterial origin constitute a third group.

A.—DISORDERS OF SECRETION.

1. Influence of Disorders of Secretion upon Gastric Digestion.

It is well known that the secretion of hydrochloric acid in disease may be either diminished (hypacidity), sometimes even completely absent (anacidity), or increased (hyperacidity), in which case there is not infrequently an increase in the secretion of water also (hypersecretion).

Generally speaking, the secretion of the ferments pepsin and rennin runs parallel with that of the hydrochloric acid, so that in many cases hypacidity coincides with hypochylia, anacidity with achylia, and hyperacidity with hyperchylia [Hammerschlag (12), Oppler (13), Guitl (14)]. This parallelism is not constant, however ; wide departures from it occur [Troller (15), Kövesi (16), Schorlemmer (17), Nirenstein and Schiff (18)], and there are consequently all manner of differences in the clinical aspects of different cases. It may be mentioned in particular that, according to Troller, in those very common cases of functional anacidity the secretion of pepsin and of rennin is often only latent—that is to say, it can at once be excited by the administration of hydrochloric acid by the mouth. In cases of hyperacidity, on the other hand, the secretion of pepsin may be completely absent. It is not a surprise, therefore, if, as Fleischer (19) and Boas (20) have pointed out, protein digestion is sometimes much delayed when the hydrochloric acid is present in excess.

Apart from these cases, gastric digestion in the presence of *increased quantities of hydrochloric acid* usually takes place as follows : The protein is rapidly and completely dissolved and digested [up to 92 per cent. of minced beef (6)], whilst saccharification of starch, which in the early stages of gastric digestion should still continue under the influence of saliva that has been swallowed, is quickly checked, ceasing entirely when the hydrochloric acid reaches 0·12 per cent. [Riegel (21)]. As regards the splitting up of the fats, Volhard (11) was able to show a decrease in one case ; he finds in this the cause of the instinctive repugnance to fat so often observed in those who suffer from hyperacidity. The stomach contents recovered after either a test-dinner or a test-breakfast have a consistency resembling that of thick soup ; this is due to the prompt

[1] More recent researches (Boldireff, *Ctb. f. Phys.*, 1904, No. 15 ; Meyer, *Kongr. i. Med.*, 1905) throw doubt upon the existence of this ferment, and ascribe its action to regurgitated succus entericus.

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chemical disintegration of the meat and bread by digestion of the connective tissue and the coverings of the gluten. This breaking up of bread into fine particles is in strong contrast to the poor way in which starch, the chief constituent of bread, is itself digested; the finely-divided solid residue after a test-breakfast is copious.

When there is *diminished secretion of hydrochloric acid*, it is the digestion of protein which particularly suffers, especially that of connective tissue [Schmidt] and of gluten.[1] In consequence of this the disintegration of the pieces of meat and bread in the food swallowed is imperfect. This incomplete disintegration naturally checks the process of digestion still further, and, indeed, not only that of the proteins, but also that of the bread-stuffs, notwithstanding the fact that the saccharification of starch is favoured by the scarcity of hydrochloric acid. The food therefore reaches the intestine in a state of little or no preparation, and a great increase of work is thus thrown upon the bowel. When the hydrochloric acid secretion is in abeyance, decomposition processes are set up in the stomach contents; these are intensified when there is coincident diminution in motility. Small quantities of protein can still be peptonized, owing to the formation of lactic acid, provided that the secretion of pepsin is not entirely interfered with at the same time; but this compensation is so incomplete that it is insignificant in comparison to normal digestion.

In regard to the *influence which disturbances of secretion exert upon the motor activity of the stomach*, this rule holds good: that increased production of acids delays the passage of ingesta into the duodenum; diminution or absence of acids hasten such passage. This aphorism is, however, to be accepted with caution, in that it assumes that the disturbance of secretion is the primary lesion, and that secretion and motility are not affected simultaneously, as in cases of carcinoma. The causal connection between these two functions is by no means obvious in many cases. Whereas the occurrence of hyp- and anacidity is commonly assumed to be primary in gastritis, in functional and in organic achylia certain investigators regard the hyperacidity in the majority of cases as secondary to motor disturbances. This is more than probable in those forms which are associated with hypersecretion [Schreiber (22), Hayem (23)], and very probable, though not absolutely certain, in many cases of simple ulcer of the stomach; the acid stomach catarrh of Jaworski (24) and primary nervous hyperacidity have long since established their right to special places in pathology.

It is none the less a striking fact that accelerated emptying of the stomach from hypermotility occurs almost constantly in achylia, and it is difficult to regard this in any other light than as an act of compensation for the delay in the processes of food disintegration.[2] On the other hand, it is well established that a high percentage of hydrochloric acid

[1] An exception to this rule occurs in carcinoma, because here an autolytic ferment from the cancer tissue passes into the stomach contents. For further information on this point, see section on Carcinoma below.

[2] Elsner (*D. Med. W.*, 1904, No. 42) has lately contested this hypermotility on the results of experiments in which he recovered the entire gastric contents and measured the amount of sediment.

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readily excites spasm of the pylorus, and thus delays emptying of the stomach.

According to the researches of Strauss (72), *resorption from the stomach and the "Verdünnungssekretion"* are not impaired, even in complete achylia.

The question of the *decomposition processes which ensue upon disturbances of secretion* will be considered fully below.

2. Influence of Disorders of Secretion upon Intestinal Digestion.

That the different digestive glands are influenced by one another was first demonstrated by Sticker and Biernacki (25), who showed that the secretory activity of the stomach was prejudicially affected by defective secretion of saliva—as in rectal feeding, for example—or by preventing saliva from reaching the stomach. Pawlow (5) has more recently discovered the *close relationship between the hydrochloric acid of the gastric juice and the secretion of the pancreas.* He states definitely that this hydrochloric acid is the most powerful stimulant we know for promoting the flow of pancreatic juice. The experiments of von Dolinsky (26) and Wertheimer and Lepage (27) show that in all probability hyperacidity is associated with deficiency of pancreatic juice, hyperacidity the reverse. Whether this be actually so or not it is difficult to say, so little is known as to the variations in the digestive phenomena that occur in the small intestine. According to Linossier (28), it is possible that in hyperacidity the strongly acid chyme destroys the trypsin and stops the function of the pancreas, in consequence of which the patients waste away, as one so commonly sees in practice. Just as in the earlier investigations of Boas (29), these conclusions are based too much upon experiments *in vitro* and upon theoretical deductions, and cannot yet be accepted in the pathology of the living body.

We know nothing about the changes which occur in the bile and in the succus entericus as the result of disorders of gastric secretion.

Motility, resorption, and disintegration processes in the intestine may be much altered by disorders of secretion in the stomach. Since it has hitherto been impossible to draw a sharp line of demarcation between the processes involved in these three closely interdependent functions, they may at present be considered together.[1] Are diarrhœa and constipation ever directly due to errors of hydrochloric acid secretion? Oppler (30) and Einhorn (31) were the first to show conclusively that there are diarrhœas and obstipations of purely gastric origin, and that the former are usually the result of diminished, the latter of increased, hydrochloric acid secretion. Further experience has established this as a general rule, it is true, but has also shown us that there are certain exceptions. Einhorn (32) has himself communicated some more recent observations on cases in which—exactly the reverse of what is more usual—achylia was associated with constipation and hyperacidity with diarrhœa. Schütz (33), who has gone

[1] The relation of motility of the intestine to resorption and to disintegration processes is discussed in the following section.

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very fully into these conditions, rightly remarks that it is not a question of any necessary sequence of events, but rather of certain complications which arise only in a limited percentage of all cases, and even in these often only temporarily. According to his calculations, at most one-third of all those who suffer from achylia have bowel disturbance at the same time. Schütz noticed that diarrhœa occurred in association with stomach disorders which were less secretory than motor—for example, after atony with only slight diminution of acidity, in which case there can be no question of a disordered secretion having a specific action. My own experiences (34) completely agree with those of Schütz, and I prefer to class these various conditions broadly together as gastrogenous diarrhœas or obstipations, as the case may be. The exact mode of origin of these gastrogenous disorders of the intestines is uncertain. If we class the latter broadly together, it is not possible to accept the first explanation which suggests itself—namely, that they are to be attributed to the failure of the disinfecting action of the hydrochloric acid in the stomach.

In order to establish this point we must retrace our steps a little. It has long been known that hydrochloric acid solution of the strength present in the gastric juice has active bactericidal properties [Bunge, Hamburger (35)]. One must not, however, assume that it can exert this power to the same extent in the living stomach as it does *in vitro*. At the outset this is improbable, because the hydrochloric acid only gradually penetrates the mass to be digested, and in the earlier part of digestion becomes combined with protein molecules; furthermore, the propulsion of the gastric contents into the duodenum begins early [Schütz (36)]. Macfadyen (37) actually found that almost all spores and various bacteria remained capable of cultivation after passage through the stomach, and Schütz was able to establish this for the vibrio of Metchnikoff. The disinfecting action of the hydrochloric acid in the stomach is therefore limited. It is even possible, as we know, for decomposition to occur in the presence of hydrochloric acid, if the gastric contents stagnate on account of motor insufficiency (*vide infra*). Nevertheless, it cannot be doubted that deficiency of hydrochloric acid favours the occurrence of fermentation in the stomach, and increases the danger of pathogenic organisms, such as cholera bacilli, passing alive into the intestine [Koch (38)].

At the same time this is very far from saying that it exerts any great influence over putrefactive processes in the bowel; for the bacterial flora of the intestine—at least, under normal conditions and within wide limits—is entirely independent of the varieties of bacteria swallowed with the food. The teaching in regard to the disinfectant action of the hydrochloric acid of the stomach upon the intestinal canal was originally based upon Baumann's test, which consists in measuring the amount of putrefaction in the bowel by the quantity of ethyl-sulphuric acid excreted in the urine. By this method various observers [Kast, Wasbutzki, Biernacki, Stadelmann, Rost, Mester, Ziemke (39)] believed that they had definitely proved that exhaustion or neutralization of the gastric hydrochloric acid caused an increase in intestinal putrefaction; and that, conversely, in-

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creased hydrochloric acid secretion suppressed the putrefaction. Their experimental method is open to many objections, and von Noorden (40), who adheres firmly to clinical observations, came to exactly opposite conclusions. To use his own words, he says: "Abgesehen von der Erhaltung zufällig eintretender pathogener Keime und der Etablierung wahrer Faülnis im Magen selbst—Salzsäuregehalt oder Salzsäuremangel im Magen keinen Einfluss auf den Ablauf der natürlichen Faülnisprozesse in Darm."

Grave doubts as to the reliability of Baumann's test have arisen of late years. It has been concluded that, even if the ethyl sulphuric acids of the urine—for example, in the indican test—afford a measure of the greater part of the decomposition products of protein, yet they do not include them all—the oxy-acids and the substances which combine with glycuronic acid, for example. Further, it is obvious that Baumann does not account for those putrefactive products which are eliminated in the fæces; yet the amount thus excreted is by no means small, and, indeed, is often in inverse ratio to the amount eliminated in the urine. Schütz (36), who has laid stress on these sources of error, further points out that an unknown quantity of indol and skatol may be lost by oxidation in passing to the urine after absorption from the intestinal canal, whilst the varying secretory activity of the kidneys must be taken into account. Finally, it must not be forgotten that the breaking down of protein under the influences of different bacteria by no means always follows the same course, and the end-products are not always the same [Fr. Müller (41)].

Other means of measuring putrefaction in the bowel have therefore been elaborated. In the following chapter this will be more fully considered; for the present only those points which are of importance to the question under discussion are included. After unavailing attempts to estimate the number of intestinal bacteria by cultivation of fresh fæces, or by counting stained preparations [Sucksdorff, Stern, Alex. Klein, Cornelia de Lange, and others (42)], Strasburger (43) propounded a method of determining by weight the total quantity of dead and living bacteria in the fæces. He found that the quantity is always high in diarrhœa, whilst in constipation it often falls very low. This rule holds good for gastrogenous diarrhœas and obstipations also, so that we may conclude that in achylia the growth of putrefactive organisms in the intestine is exuberant, and that in hyperchylia it is the reverse. Can we conclude that the hydrochloric acid is actually the cause of this? The question must remain unanswered, notwithstanding the fact that Schütz several times found the same organisms in the fæces as were growing in the gastric contents of his patients.

The net result of this discussion is that the part played by the hydrochloric acid of the stomach in the origin of gastrogenous disorders of the intestine is still obscure. It is quite certain that there is no simple relationship between the hydrochloric acid and the intestinal putrefaction. As has been mentioned, secondary diarrhœa occurs even with normal or increased hydrochloric acid in the stomach. It cannot, however, be denied that stomach conditions can co-operate in producing fermentation and putrefaction. When the chemical and motor activities of the

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stomach are inefficient, putrefactive organisms can establish themselves more easily in this viscus, and pass through it uninjured. It is, however, doubtful whether these conditions are by themselves enough to account for the occurrence of gastrogenous disorders of the intestine.

Schütz propounds the view that the increased demands made upon the small intestine in consequence of gastric insufficiency gradually lead to inefficiency of the bowel too. According to his researches (36), the succus entericus, even without the assistance of the gastric juice, possesses antiseptic properties; defects in the latter would add themselves to diminution of the gastric antisepsis, and favour the occurrence of still greater decomposition in the bowel. In addition to this, the pancreatic secretion might be lessened in the absence of proper stimulation by the hydrochloric acid (*vide* p. 172). This secondary insufficiency of digestion in the small intestine has not hitherto been proved, nor can it be, in the present state of knowledge as to the functions of the bowel.

My own explanation (44) of gastrogenous diarrhœas receives firmer support from arguments based upon inefficient digestion of connective tissue, expressed in a general way by the imperfect disintegration of the food in a stomach which is doing its work badly. The "meat-test" I suggested, which has been verified by Zweig (45) and Strauss (26), established the fact that even with very slight degrees of insufficiency of secretion, but also in other disturbances of function, such as atony, undigested residues of connective tissue appear in the fæces; indeed, this may be used as a delicate test for all sorts of different disorders of the stomach, some of which may not always be apparent. As has been already mentioned, the stomach is the only part of the alimentary tract in which raw or smoked or incompletely cooked connective tissue is dissolved. Should this dissolving process be wanting or incomplete, not only will the whole of the connective tissue of the ingesta be carried through the intestine as ballast, but also the further digestion of the protein and fat bound up in and surrounded by connective tissue will be inhibited. This may lead to a flesh- or fat-lientery [Brink (47)]. When unabsorbed constituents of the food remain in the bowel, the danger of severe putrefactive processes setting in is increased, for the number and variety of intestinal bacteria fluctuates in direct ratio to the quantity and quality of the food residue at their disposal. Whether the putrefactive organisms begin to grow in the stomach itself, or only in the lower part of the small intestine, the end-effect, the diarrhœa, is the same. Such an explanation makes it unnecessary to assume a special secondary insufficiency of digestion in the bowel, or any mechanical excitation of the mucosa of the small intestine by ingesta that have been incompletely broken up, although the latter may be an additioual factor. This theory of mine is supported by von Jabora (*M. Med. W.*, 1904, No. 20).

From the above discussion it appears that the ultimate cause of gastrogenous diarrhœa is the multiplication of fermentative and putrefactive bacteria, but that for this to occur the bowel must become overburdened with insufficiently prepared food-stuffs, or, in the words of Moritz, the stomach ceases to be an efficient protector to the intestine. It is easy to understand why this diarrhœa is not a constant accompani-

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ment of an inefficient stomach : as long as the patient prepares his food properly—above all else, cuts it up well—before eating, it need never occur. In practice it is well known that those who suffer from achylia may remain free from intestinal complications if they observe these rules, but that they are very sensitive to slight deficiencies in cooking.

Hitherto we have spoken almost entirely of gastrogenous diarrhœas ; it must be reiterated, however, that constipation also often has a gastric origin. As a rule, constipation accompanies hyperacidity ; now and then it ensues upon achylia. The explanation of this is clear. In cases of hyperacidity it depends upon a diminution in the putrefactive processes in the bowel, owing to good disintegration and disinfection of the food in the stomach. This theory is supported by the researches of Strasburger (43), who showed that in obstipation, and particularly in gastrogenous obstipation, there was a decrease in the number of bacteria in the intestine.

3. Influence of Disorders of Secretion upon the Composition of the Blood and Urine.[1]

(*a*) The *Alkalinity of the Blood* is normally, but not constantly, increased at the height of gastric digestion, when the hydrochloric acid secretion is abundant [Canard, Baldi, Sticker and Hübner, Drouin, von Noorden (48)]. Von Noorden (49), using the Landois-Jaksch method, made examinations of the blood before and after meals in patients who had anomalies of secretion. He found that there was no great departure from the above rule, except that in hyperacidity the increased alkalinity was particularly well marked.

In a great many of those who have stomach disorders there is a diminution in the hæmoglobin and in the red corpuscles of the blood. This anæmia usually has the character of a secondary anæmia, and is very probably due to constantly recurring small hemorrhages into the stomach [Boas, Boas and Kochmann, Schloss (50)].

In agreement with this view is the fact that it is far more common when an ulcer is present, whether simple or malignant, than in other gastric affections.[2]

Uncomplicated disorders of secretion have apparently no influence upon morphological changes in the blood [Blindermann (51)], although some writers [E. Gravitz (52)] maintain that there is a causal relationship between achylia and severe, even pernicious, anæmia. This is fully discussed in the chapter upon intestinal auto-intoxications, but it may here be mentioned that the inanition which ensues upon gastric disorders may in itself be a cause of anæmia.

(*b*) *Disorders of Gastric Secretion influence the Urine chiefly as regards its Reaction.*—The changes which different amounts of hydrochloric acid secretion produce here are much more obvious than they are in the blood.

As Bence-Jones (53) showed, the acidity of the urine diminishes for some hours after a meal. The reaction may become neutral or even alka-

[1] For the specific effects of carcinoma, see the chapter on Carcinoma.
[2] In regard to the anæmia of carcinoma, see the chapter on Carcinoma.

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line at the height of digestion, three hours after a small meal, five to six hours after a large one. This, as Bence-Jones pointed out, is simply the result of withdrawal of acid from the blood [Maly, Quincke, Stein (54)]. It is seen most clearly after the chief meal of the day. If this be taken at midday, the phenomenon is often absent after the supper of the same day on account of the reaction after the midday meal and the acids set free by the splitting up of absorbed protein. By reason of the rapid passage of acids and alkalis into the urine the alkalinity of the blood is kept approximately constant, notwithstanding the varying demands made upon it by the alimentary canal [Freudberg (55)]. It thus comes about that the reaction of the blood follows the changes of that of the urine either not at all or only in a very slight degree. The diminished acidity of the urine is most marked upon mixed diet; it is accentuated by taking alkalis with the food, and minimized by taking hydrochloric acid.

When the secretory processes are out of order, it is well established that the diminution in urine acidity after eating is slight or absent when gastric digestion takes place without demonstrable hydrochloric acid in the stomach. This is so in gastritis, achylia, carcinoma [Leube, Sticker and Hübner, Ringstedt (57)]. The urine may become alkaline when the gastric juice is abnormally rich in acid [Sticker and Hübner], or when there is much vomiting of gastric contents containing hydrochloric acid [Quincke]. When hyperacidity is combined with marked motor inefficiency of the stomach, the urine may become constantly alkaline [Klemperer (58)].

Uncomplicated disorders of secretion have very little effect upon the quantity of chlorides in the urine, although Jaworski and Glucinski (59) have shown that even simple hyperacidity may cause a diminution in the chlorides excreted. This becomes more obvious when the increased secretion of hydrochloric acid into the stomach is accompanied either by motor inefficiency and delayed emptying into the duodenum, or by vomiting [Rosenthal (60)]. It may be mentioned here that it is important to consider carefully the intake of food before speaking of a diminution of the chlorides in the urine in stomach disorders. Patients whose stomachs are out of order often eat less than do healthy persons, and their food is usually poor in salts. It is therefore not to be wondered at that their urine seldom contains the normal 12·15 grammes NaCl per diem. Von Noorden and Stroh (61) regard 6, 8, and 11 grammes as normal in those who have gastric troubles. One can only speak of the diminution being pathological when the excretion of NaCl falls considerably below this, so that the silver nitrate test only gives a faint cloud in the urine.

In contrast to the chlorides, the phosphates are often increased in hyperchlorhydria [Gubler and Robin (62)]. According to Robin, this increase is more constant than is the diminution in chlorides. One would like to know how the excretion of phosphates in the fæces behaves at the same time.[1]

[1] Loeb (*Zt. klin. M.*, 1905, lvi., p. 100) finds that, in hyperacidity with vomiting, the ammonia excreted in the urine diminishes, no doubt because more alkali than usual remains to be dealt with in the body.

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The gastric ferments, pepsin and rennin, normally pass into the urine [Brücke, Leo, Stadelmann, Holovtschiner, Boas, and others (63)], but hitherto no constant relation between the quantities of these bodies in the urine and the anomalies of gastric secretion has been established. Leo was originally inclined to regard the absence of pepsin from the urine as of diagnostic value in cases of carcinoma, but later he found that it can be very much diminished without apparent cause. Similarly Edgar Gans and Bendersky (64) found the peptic activity of the urine to be sometimes absent notwithstanding a well-maintained or even increased secretion of gastric juice, whilst in cases of severe gastric catarrh, on the other hand, when the stomach contents contained neither pepsin nor pepsinogen, they found the peptic activity of the urine increased. In the face of these observations, it is not possible to attach any real clinical importance to the paucity of pepsin in the urine in cases of achylia and carcinoma, which was observed by Brunner and Friedberger (65).

Of abnormal constituents of the urine, a brief notice must be taken of the occurrence of albumin and albumose in various stomach affections, although these are not strictly limited to disorders of secretion. According to von Noorden (66), small quantities of albumin are not infrequently found in patients whose stomachs are out of order, particularly those whose trouble is advanced. It is only one of the phenomena of inanition. Somewhat larger quantities occur after acute attacks of gastric colic in simple ulcer, and particularly after severe hæmatemesis. Albumoses occur in simple ulcer and in breaking down carcinoma of the stomach, as they do in all cases of ulceration of the alimentary tract [Maixner, Pacanowski, O. Brieger, von Aldor (67)], but they have no diagnostic significance.

4. Influence of Disorders of Secretion upon the Resorption of Food, and upon Metabolism and Nutrition as a Whole.

Ogata (68) and De Filippi (69) showed that in dogs the stomach could be entirely shut off from the alimentary canal without causing any interference with the resorption of nourishment or with metabolism as a whole, with the single exception that all raw connective tissue was undigested and reappeared in the fæces (*vide* p. 175). Since then Schlatter and Hofmann have proved that this is true for man also. Their observations were made upon a female patient whose entire stomach had been removed by operation. Schlatter's patient, an elderly woman, increased 4·4 kilogrammes in weight in two months. She showed a normal resorption of her food without any increase in intestinal putrefaction. Pepsin was absent from the urine.

Previous to Schlatter, von Noorden (71) had investigated the question of food resorption in cases where the chemical changes in the stomach were pathological. In thirteen serial experiments he showed that, in patients who were secreting extremely little hydrochloric acid, no more than usual was lost per rectum out of considerable quantities of protein (100 to 130 grammes) and fat (64 to 126 grammes) given by the mouth.

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The food consisted of milk, raw, boiled, and roasted mutton, ham, eggs, wheaten bread, biscuit, butter, cod-liver oil, and so on. Von Noorden recovered, upon the average, 7·3 per cent. nitrogen, 7·1 per cent. of fat, and 1 to 1·5 per cent. of carbohydrate in the fæces. He remarks that "man bessere Ausnützungswerte auch nicht erhalten hätte, wenn im Magen Salzsaüreeinwirkung stattgefunden hätte." His view is that the digesting powers of the intestine are able to compensate for secretory insufficiency in the stomach, provided that the stomach empties itself completely into the intestine and that no diarrhœa be present. I should like to add, as a further condition, that no raw or smoked meat requiring connective tissue digestion should be eaten.

Von Noorden's researches have since been confirmed by numerous other observers who have investigated patients with achylia (72). Amongst all the results that have been published, those of von Stejskal and Erben alone have shown resorption to be impaired to any obvious extent. Their patient lost 17 per cent. nitrogen, 13·5 per cent. fat, and 6 per cent. carbohydrate per rectum; the motions, however, were abnormally fluid.[1] Strauss's observations clearly demonstrate that the power of the intestine to digest is considerable. A patient who had achylia and pernicious anæmia lost only 9 per cent. nitrogen and 7·8 per cent. fat when his motions were fluid but thick, but when diarrhœa set in he lost 23 per cent. nitrogen and 14·5 per cent. fat. In another case the conditions were similar. Both these patients put on flesh in spite of their temporary diarrhœas, and the same was the case in a patient of Stejskal's and Erben's. These metabolism results are in perfect agreement with what may be observed clinically every day. Subacidity and achylia are very often met with in well-nourished people. Even after these disorders have existed for years the invalids do not waste appreciably, provided no complications arise, such as motor disturbances, carcinoma, or an upset of the intestinal digestion. Gravitz's assertion (50) that absence of gastric digestion over a long period may by itself give rise to fatal cachexia requires confirmation. The only general disease which, without there being any necessary emaciation, is at all frequently met with in achylia is anæmia of the pernicious type. In all probability achylia does not itself produce pernicious anæmia. It is more likely that both have a common cause. This is discussed under the headings of Intestine and Carcinoma.

Some other results which Strauss obtained in his careful metabolism researches in apepsia gastrica, with and without pernicious anæmia, may now be cited. He found that the excretion of uric acid in the urine remains normal in pernicious anæmia unless there are complications. The ammonia excretion was normal. The metabolism of phosphoric acid and of sodium chloride was not increased. Finally, Strauss determined the ethyl-sulphuric acid of the urine, and its toxicity [Bouchard], and endeavoured by Griffith's method to recover certain ptomaines that were present. Even these last afforded no evidence of any pathological disturbance of metabolism (see also Intestine, decomposition in).

[1] According to von Jabora (*Zt. klin. M.*, 1904, liii., p. 460), there is always an impaired resorption in achylia whenever the stomach is given a maximum of work to do.

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Hyperacidity of the Gastric Juice.—Von Noorden (71) records that, of the food taken by the mouth and not evacuated by vomiting or purging, 8·6 per cent. nitrogen and 5·3 per cent. fat were eliminated in the fæces. These figures must be regarded as perfectly normal under the circumstances. I am able to add to them some that are similar. For metabolism to be normal in cases of hyperacidity it is essential that the function of the bowel should be unimpaired, and that the food should pass into the intestine completely and at the proper time. This last condition is less often fulfilled in these cases than it is in achylia because the hyperacidity readily produces pyloric spasm, and atony soon follows. The occurrence of a peptic ulcer is favoured and its healing hindered [Sticker, Korczynski, and Jaworski (73)]. Lastly, the hyperacidity very often interferes with proper ingestion of food, because it leads to a repugnance to fat, or causes painful sensations or even vomiting during digestion. Many cases of this sort, even such as have quite uncomplicated hyperacidity, lose flesh. In order to explain these cases there is no need to invoke a hypothetical destruction of trypsin by the highly acid chyme, as Linoissier (28) has done.

The general conclusion that can be drawn from the discussion in this section is that disorders of gastric secretion, provided they do not prejudice the intake of food, and provided they be not complicated by motor disturbances of the stomach, or by disorders of the intestine, do not appreciably affect metabolism and the resorption of food, except that of connective tissue in cases of achylia.

B.—MOTOR DISTURBANCES.

1. Influence of Motor Disturbances upon Gastric Digestion.

The motor disturbances may be divided into three groups: (1) Vomiting; (2) hypermotility, with accelerated emptying into the duodenum; (3) motor insufficiency. Of these, vomiting, a well-known symptom of all sorts of stomach affections, such as simple ulcer, carcinoma, hyperacidity, and so on, naturally has no influence upon actual digestion in the stomach. Hypermotility may interrupt gastric digestion unduly soon, but the condition occurs most commonly in achylia, in which hardly any digestion occurs in the stomach at all.

Under the term "motor insufficiency" there may be grouped all those disorders in which the muscular coat of the stomach is no longer capable of propelling the ingesta into the duodenum at the proper time, and this whether the trouble be functional or the result of real obstruction at the pylorus. The consequences of motor insufficiency may be either disorders of secretion, or decomposition, or both. As regards the former, simple pathological conditions which hinder emptying of the stomach, such as ulcers and cicatrices, spasm of the pylorus and simple atony, are usually associated with hyperacidity and ultimately with hypersecretion also, whereas, with malignant affections, such as carcinoma, the secretion is diminished. In both groups of cases however,

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we must be careful to distinguish between cause and effect. As we have mentioned already, primary hyperacidity may lead to pyloric spasm, and so to motor insufficiency. On the other hand, the growth of a carcinoma is usually detrimental to both glandular structure and muscle wall simultaneously. There are, of course, certain exceptions. A circumscribed cancer of the pylorus, for example, may for a while behave just like a cicatricial stenosis, and cause increased secretion of acid. Nevertheless, it is certain that motor insufficiency causing no disorder of secretion is a rare phenomenon—rarer, at all events, than disorders of secretion without motor disturbances.

Motor insufficiency is even more constantly followed by decomposition of the gastric contents, so much so that it may be designated the chief cause of such decomposition (see Section C, p. 185).

The higher degrees of motor insufficiency—those which are associated with dilatation and stagnation—have a very considerable effect upon resorption through the stomach wall. Even under normal conditions only small quantities of dissolved food-stuffs are absorbed; the pathologically dilated stomach absorbs practically none at all. Potassium iodide appears in the saliva and urine in ten to twelve minutes after administration by the mouth in a healthy fasting man. In patients with dilated stomach the iodide cannot be detected in these secretions until a much longer time has elapsed, sometimes an hour or more, showing that resorption is much delayed (75).

2. Influence of Motor Disturbances upon Intestinal Digestion.

Delay and acceleration of the emptying of the gastric contents into the duodenum have by themselves no influence upon intestinal digestion. They are only of importance in so far as they are associated with disorders of secretion or with decomposition processes. The same holds good for these as has already been described in Section A, 2, in regard to gastrogenous disturbances of the bowel. Foucaud's (76) assertion that delayed emptying causes constipation, accelerated diarrhœa, is to be interpreted in the same way.

3. Influence of Motor Disturbances upon the Condition of the Blood and of the Urine.[1]

Formerly there was never any idea that a relationship existed between disturbances in the mechanics of the stomach and changes in the blood—apart, at least, from the anæmia which arises from the inanition caused by pyloric obstruction. Meinert (77), however, has recently put forward the view that chlorosis is a constant result of displacement of the stomach downwards, or into a vertical position—gastroptosis. He believes that the cause of chlorotic anæmia is to be sought for in this anomaly, which is frequently brought about by the pressure of corsets, and is often associated with atony. The discussion which Meinert's publication called forth [Agéron, Meltzing, Brüggemann, Leo, Kuttner and Dyer, von Noorden

[1] With regard to the specific action of carcinoma, see the chapter on Carcinoma.

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(78)] turned upon the question of relationship between atony and motor insufficiency [Bial, Stiller, Elsner, Boas (79)], and threw light upon many points. The main conclusions that may be accepted are as follows :

(1) Atony of the stomach is a condition of sluggishness and abnormal extensibility of the muscle wall, which is very often, but not always, associated with delay in emptying, or motor insufficiency of the first degree. It can occur with or without a dropping of the whole stomach, especially of its lesser curvature. Nevertheless, the extent of the gastroptosis is not directly proportional to the atony, although both conditions are so often associated together. Gastroptosis may be congenital ; it may follow repeated child-bearing, owing to weakening of the abdominal wall ; it may be due to tight lacing ; it is occasionally found in chlorosis, but is no necessary accompaniment of it. Much more common is it to find atony and chlorosis together without gastroptosis or motor insufficiency. Here, however, the causal relationship is reversed ; chlorosis is the cause, and atony the result [von Noorden (78)]. Evidence of this is afforded by the way in which other forms of impoverished blood and various debilitating general diseases, neurasthenia, long-standing gastric catarrh, and, indeed, all conditions which favour a functional decrease in muscular strength, may bring atony in their train. It is, therefore, unnecessary for there to be any simultaneous obstruction at the pylorus, whether anatomical or spasmodic, although we must remember that atony may be the first symptom of a stenosis long before there is definite motor insufficiency (Boas).

(2) The quantity of urine may fall when there are motor disturbances, particularly when there is much vomiting, or when there is marked ectasia with diminished water absorption. Under the latter conditions it is not uncommon to find only 300 to 400 c.c. passed by an adult man in twenty-four hours. Increased diuresis after previous diminution is a favourable sign. It shows that the resorptive power of the stomach itself has improved, or else that the chyme is more completely propelled into the duodenum.

(3) As regards the acidity of the urine, the facts already mentioned may be referred to—namely, that the urine may become alkaline after the vomiting of gastric contents, rich in hydrochloric acid, or when these contents stagnate in the stomach as the result of pyloric obstruction.

(4) The sodium chloride falls considerably under these same circumstances ; it may become so small in amount that silver nitrate solution hardly clouds the urine. The reason for this is twofold : on the one hand, little sodium chloride is absorbed ; on the other hand, the body is loth to part with chlorides, as it is in all forms of inanition. An increase in the chlorides is always a good sign, therefore. It indicates even better than does the increased diuresis that food is again being absorbed (80).

In simple pyloric stenosis poor resorption coincides with plentiful secretion of hydrochloric acid into the stomach. In carcinoma of the pylorus only the first of these two factors influences the diminution of chlorides in the urine. Glucinski (81) therefore thought that marked decrease in urinary chlorides must favour a diagnosis of simple stenosis. This, however, has not yet been confirmed, for in pyloric obstruction of

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both sorts the impaired resorption of food diminishes the chlorides to such a degree that they cannot be much further decreased when chlorine is being secreted in the stomach at the same time. Stroh's (82) analyses throw some light upon this. He found that the daily amount of chloride excretion was 0·2 gramme to 1·5 grammes in one case where stomach dilatation was associated with copious secretion of hydrochloric acid, 0·16 gramme to 0·8 gramme in another. When dilatation was associated with absence of hydrochloric acid in a case of carcinoma he found in one case 0·34 gramme to 3·4 grammes sodium chloride, in another, 0·24 gramme to 1·7 grammes, and in a third 0·66 gramme. There is, therefore, no assistance in differential diagnosis to be gained from these chloride estimations.

It must be remembered that the body, at the same time that it reduces the chloride excreted in the urine to a minimum, also loses considerable amounts of chlorine by vomiting when a dilated stomach is associated with hypersecretion. It has been suggested that the chloride impoverishment of the body, either by itself or combined with dehydration of the tissues by deficient resorption of water, may be the explanation of tetany in stomach affections (see the following section).

There is still one other point of interest as regards both the secretory and the motor aspects of the affections under discussion. Cahn (83) showed that when dogs were given food deficient in chlorides the hydrochloric acid disappeared from the gastric juice as soon as the chlorides in the urine were found markedly diminished. On the other hand, the patients who have hypersecretion still continue to secrete large quantities of chlorine into the stomach for years, long after the chloride excretion in the urine has fallen to a mere trace. This shows with what energy this peculiar pathological process of hypersecretion, for which there is as yet no reliable explanation, robs the body of one of its most important constituents. The peculiarity of this pathological process stands out still more distinctly in that, in patients who for other reasons take little nourishment, the stomach suspends its secretion of hydrochloric acid long before the last stages of inanition are reached, thus agreeing completely with what Cahn observed in the dog [von Noorden (84)].

4. Influence of Motor Disturbances upon General Nutrition and Metabolism.[1]

The effects of motor disturbances upon general nutrition are much more serious than are disorders of gastric secretion. This is true both for vomiting, at least in its more obstinate forms, and for delayed or suspended emptying into the intestine—that is to say, motor insufficiency. The exception is hypermotility, which has no influence upon nutrition at all. All the other conditions except this one lead to inanition, and they do so in the same way, though in varying degrees. In the case of persistent vomiting without other complications—for example, in gastric crises, hyperemesis gravidarum, and so on—the reason is very simple. The total quantity of food taken is diminished, and malnutrition follows. In cases

[1] For the specific action of carcinoma, see the chapter on Carcinoma.

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of pyloric obstruction the food may remain lying in the stomach, it is true, but it does not pass into the bowel properly. Now, the stomach is not itself adapted for resorption, and even the little resorptive power it has is still further weakened by dilatation and stagnation. Nutrition therefore suffers almost as much as if the food had not been taken at all. In addition to this, appetite is very poor in these cases in striking contrast to the thirst, which is great and persistent. The food residues which accumulate cause sensations of tightness and of fullness; they decompose, and bring the gastric mucosa into a state of chronic inflammation, which may extend to the œsophagus and mucous membrane of the mouth—hence the coated tongue. Vomiting occurs from time to time. After such relief a temporary feeling of intense hunger sets in, perhaps; the patient swallows great quantities of all sorts of food in quick succession, until the feeling of fullness returns and decomposition sets in once more.

Sometimes no food is taken because of acute pain—for example, in simple ulcer. How limited the spontaneous taking of food may be under such conditions is illustrated by certain figures of von Noorden's (85): on a two days' average the nutriment taken by patients of their own free will, uncontrolled by the physician, in five severe cases of gastrectasis (three with ulcer, two with carcinoma of the pylorus) could yield only 12 to 19 calories per kilogramme body-weight per diem; even of this no inconsiderable part was vomited.

It is obvious how great is the danger of gradual starvation to which these patients are exposed. They emaciate slowly but steadily to an extreme degree. Their tissues dry up, but even in this pitiful condition they often drag on for an astounding length of time before they die. The explanation of this is that the change is seldom sudden, but is slowly progressive, so that the body has time to accommodate itself to its altered state of nutrition. The output in the form of warmth, motion, muscular work, is cut down to a minimum. This state of *vita minima* makes one think that the cell metabolism must have become different to that of health—an idea, however, which has no exact observations to support it.

Further details concerning inanition appear in an earlier chapter. Nothing could be mentioned here that is not practically the same as is met with in similar states of malnutrition due to other causes. There are the occurrence of acetone and aceto-acetic acid in the excreta, traces of albumin in the urine, progressive anæmia, and so on. Kussmaul's view that tetany and other nervous phenomena depend on dehydration of the tissues will be considered later. It may here be mentioned that intense inanition seldom occurs in cases of simple atony without stenosis, even if part of the gastric contents is regularly lost by vomiting.

C.—DECOMPOSITION.

1. Influence of Decomposition upon Gastric Digestion.

Decomposition by micro-organisms in the gastric juice affects either the carbohydrates only or else part of the proteins as well. The fats

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are either not split up by the bacteria at all, or only to a very slight extent (86).

The chief forms of carbohydrate fermentation in the stomach are :

(1) *Lactic Acid Fermentation*, by which lactose ($C_{12}H_{22}O_{11}$)—probably after transformation into two molecules of glucose ($= 2C_6H_{12}O_6$)—is split up into four molecules of lactic acid ($= 4C_3H_6O_3$). At the same time many gaseous products (CO_2, H_2) and volatile fatty acids (acetic acid, formic acid, etc.) are formed.

(2) *Butyric Acid Fermentation.*—This usually follows upon (1), the lactic acid becoming further split up into butyric acid, carbonic acid, and hydrogen, according to the following equation :

$$2(C_3H_6O_3) = C_4H_8O_2 + 2CO_2 + 2H_2.$$

(3) *Yeast Fermentation.*—By means of yeast, glucose, cane-sugar, and lactose—the last two indirectly—are split up into two molecules of ethyl alcohol and carbonic acid :

$$C_6H_{12}O_6 = 2C_2H_6O + 2CO_2.$$

At the same time small quantities of glycerin, succinic acid, acetic acid, and amyl alcohol are formed. Fermentation by sarcinæ is similar to that produced by yeast [Ehret (87)].

(4) *Acetic Acid Fermentation.*—In the stomach this does not correspond exactly with the process as seen in vinegar factories, but usually forms part of other fermentations, particularly that of butyric acid. The same is true of cellulose fermentation, which produces marsh-gas or methane (CH_4), amongst other things.

In protein putrefaction, which is never more than slight in the stomach, NH_3 and H_2S are the main products [Boas, Strauss, Dauber, and others (88)]. More complicated bodies, such as tyrosin, phenol, etc., have not hitherto been found, with the exception of indol, which Strauss once found along with H_2S. Acetone, on the other hand, has been repeatedly detected [von Jaksch, Lorenz, von Noorden (89)].

Under normal conditions of digestion no sort of putrefactive processes occur in the stomach, although the opportunity for them, owing to introduction of bacteria and media suitable for their growth, seems to be constantly afforded. It is true that small quantities of lactic acid are often present even in normal gastric contents, but it is almost always the case that these small amounts have been already present in the food [Martius and Lüttke, Boas (90)]. The factors which check the onset of putrefaction are the presence of hydrochloric acid and the motor activity of the stomach wall, the latter propelling the chyme into the intestine the moment it is ready. It is most important of all that the working of the secretory and the motor functions should be in harmony.

Even if it be not an invariable rule, yet it is exceedingly common for pathological disturbances of gastric digestion to lead to bacterial decomposition ; but whereas the latter sets in practically always in cases of motor insufficiency, even when this is only partial and accompanied by normal chemical processes, it often remains absent for a very long time in many cases where the disorder affects the secretion only. Delay in

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the emptying of the stomach at the proper time, or stagnation, is the chief factor which induces decomposition of the gastric contents. The influence of the gastric juice upon the process of decomposition is mainly qualitative. In hyperacidity with stagnation alcoholic and acetic acid fermentations usually occur. In hypacidity or achylia and stagnation lactic and butyric acid fermentations prevail. There are numerous exceptions to this rule. One can often observe that various kinds of fermentations occur in the same stomach either at the same time or on successive occasions, and this without any relationship to the quantity of hydrochloric acid present [Vanthey (91)]. Protein putrefaction is often found alongside that of carbohydrate, though the latter is always the more marked [Dauber]. Protein putrefaction in the stomach reaches a high degree only in the most exceptional cases, and only when both the secretory and the motor functions are completely out of order.

The variety of organisms present is of as little real import as is the hydrochloric acid in controlling the processes of decomposition. It is true that when the fermentation leads to much gas-production, yeasts and sarcinæ are usually abundant; when lactic acid is produced in large quantities, the well-known "long bacilli" predominate; when protein putrefaction occurs, the *Bacillus coli* is present; and so on. But careful investigation has shown that almost all the microbes here concerned are capable of originating different forms of decomposition in all sorts of different media, and that, on the other hand, the commonest forms of fermentation, such as those which lead to the formation of lactic acid and of H_2S, are by no means dependent upon any particular microbes, but can be caused by a whole host of different sorts [Miller, Dauber (92)].

It is seen, therefore, that the quality of the contents of a stomach whose motor function is defective can control the decomposition processes only in a general way. All endeavours to prove that any particular form of decomposition is characteristic of any single clinical variety of disease have hitherto been in vain. The dictum that the onset of lactic acid fermentation is a means of recognising carcinoma ventriculi early is only correct in so far as it shows both motor and secretory insufficiency to be present, and these, though they may be due to quite other causes, usually occur particularly early in cases of carcinoma. On the other hand, gaseous products of fermentation are commoner in stagnation of hyperacid gastric contents than in other conditions; volatile fatty acids, and even products of protein putrefaction, are apt to occur at the same time.

Little light has yet been thrown upon the question of how far decomposition of the gastric contents, apart from the changes they produce in the chyme, affect the secretory and motor properties of the stomach. We must here distinguish between the actions of the micro-organisms themselves and those of their products. As regards the former, we are led by general clinical experience to the belief that they seldom directly damage the stomach wall. As long as they find sufficient dead food-stuff to grow in, they do not attack the living cell; but when the food-stuffs are wanting, then they penetrate the stomach wall. The gastric mucosa is more proof against the invasion of bacteria than is almost any other tissue in the body. Of the bacterial products, only carbonic acid and

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alcohol have hitherto been experimented with in regard to their influence on gastric activity. Carbonic acid stimulates slightly both secretion and motility [Jaworski, Pentzold (92)]. Moderate quantities of alcohol have a similar action, though not in all cases [L. Wolff, Klemperer, Wolffhardt (93)]. In regard to lactic acid, we know that it can to some extent replace hydrochloric acid in the digestion of proteins by pepsin, but this it can only do very incompletely.

In agreement with these experimental results, clinical observation teaches that decomposition, as long as it keeps within certain limits, does not materially interfere with the production of hydrochloric acid. Perhaps very large amounts of hydrochloric acid which are met with in certain forms of simple stenosis may really be due to stimulation by products of decomposition. Talma (94) directly attributes the hyperchlorhydria of many patients to fermentation. When decomposition has reached a high degree, however, and when it is of long standing, its effect upon secretion is certainly inhibitory. It finally causes inflammation, and the latter interferes with cell activity. In regard to motility, decomposition makes any existing impairment still worse, by causing spasm of the pylorus [Talma]. As a matter of fact, striking examples of improvement of the mechanical working of the stomach after vomiting often occur, especially in cases of simple atony.

2. Influence of Decomposition upon Intestinal Digestion.

If the chyme be already decomposing when it reaches the duodenum, digestion in the bowel is likely to be greatly disturbed. Both the microbes themselves and their products behave as stimuli, and excite inflammation. This question is fully discussed in the section upon Gastrogenous Diarrhœa.

3. Influence of Decomposition in the Stomach upon other Organs.

The points of interest amongst the more widespread effects which result from decomposition of the contents of the human stomach are mainly those of the symptom-complexes—gastric vertigo, so-called dyspeptic asthma, and particularly tetany of gastric origin—which arise from auto-intoxications.[1]

Gastric vertigo [Trousseau] is not a sharply-defined clinical condition. It includes various feelings of giddiness, sensations of lack of clearness in the head, general feelings of languor, headache, and so on. They may occur in all manner of stomach affections, and are by no means restricted to cases of decomposition of the gastric contents, although particularly liable to be associated with it. It is therefore improbable that they have their cause in auto-intoxication, and no proof of such an assumption has yet been brought forward. By analogy with the well-known symptoms of " hydrothionæmia " [Betz, Senator (95)], one might

[1] In regard to the relations between achylia gastrica and pernicious anæmia, acetone and epilepsy, and a few other similar points, see the chapter upon Intestinal Decomposition.

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suspect H_2S to be the cause of the trouble. Although H_2S has been found in vomit, the intestine is the chief site of its formation. The amount of H_2S produced in the stomach is too small to cause any appreciable disturbance. There exists no relation between its amount and the degree of the cerebral symptoms under discussion. Even when more H_2S than usual is being produced—as, for example, in Strauss's cases (96)—the gastric vertigo is not particularly prominent. Acetone has repeatedly been met with in stagnating stomach contents by von Jaksch, Lorenz, and von Noorden (64A), but no particular effects can be ascribed to it. Finally, in regard to indol, Herter (97) believes it to produce headache, loss of appetite, and neurasthenia; but in the single case in which it has hitherto been found in the stomach these symptoms were by no means marked. Moreover, one would have expected the indol, which is normally present in, and absorbed from, the colon, to have the same effects. This is not the case. Under these circumstances, it is well to regard gastric vertigo as a reflex nervous symptom-complex, as von Leube does, until something better is discovered.

The same applies to *dyspeptic asthma*, a condition of cardiac dyspnœa, which is by no means dependent upon decomposition of the gastric contents for its occurrence. It will suffice to say that Boas (98), as the result of recent careful observations, has come to the conclusion that auto-intoxication probably plays no part in dyspeptic asthma. He believes the latter to be mainly dependent upon mechanical and reflex action upon the heart.

Tetany as a result of stomach affections was first made generally known by Kussmaul (99). In contrast to gastric vertigo and to dyspeptic asthma, tetany only occurs when the decomposition processes are severe. It is usually associated with extreme dilatation of the stomach, but such dilatation is not absolutely essential, as was shown by a case of Fleiner's (100) of achylia with severe diarrhœa. Kussmaul explains tetany as the result of dehydration of the tissues, dependent upon insufficient resorption of fluid, loss of water by vomiting, and so on. This theory is strongly upheld by Fleiner (76). Jaworski and Korczynski (24) accept it in a modified form. They believe loss of salt to be the actual cause. Another view, long ago propounded by Germain Sée, regards reflex action upon the nervous system as the cause of tetany; F. Müller (101) has recently voted in favour of this. The main supporter of the auto-intoxication theory at present is Albu (102).

The chief observations and experimental results which have been brought forward in favour of the theory of auto-intoxication are the following:

Kulneff (103) was the first to obtain toxic substances, of the nature of diamines, from the stagnant and decomposing gastric contents in cases of carcinoma. He used Brieger's method—extraction with alcohol, and precipitation with perchloride of mercury. Apparently the toxic substances were not being asborbed by his patients, for none of the latter showed any symptoms of auto-intoxication.

Bouveret and Devic (104), using the same method, investigated three cases of tetany with hyperchlorhydria, and found a spasm-producing

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substance. They were, however, doubtful as to its origin and nature. Ewald and Jacobsohn (105), and later Albu (106), obtained the salt of an alkaline body from the urine of a tetany patient, but they were unable to convince themselves that it was poisonous.

Lastly, Cassael and Bénech (107) isolated from the gastric contents, in a case of gastric fistula, a substance that was toxic for rabbits. On the other hand, several observers, particularly F. Müller (101), Strauss (108), and Gumprecht (109) have searched in vain for ptomaines and other toxines in the gastric contents of patients suffering from tetany. Gumprecht, it is true, obtained a precipitate of albumoses and salts which had a toxic action, but he could not regard it as a cause of the phenomena of auto-intoxication, because it was not found in the urine also, and therefore there was no proof that it had been absorbed.

The net result of this discussion is that the gastric auto-intoxication theory of tetany, fascinating though it is, lacks foundation. The real explanation remains to be discovered.

A word must be added concerning cases of acute fatal dilatation of the stomach. Albu (110) has put forward the view that auto-intoxication is also the cause of this rare and ill-understood affection. There is, however, no ground for this view.

4. Influence of Decomposition upon General Nutrition.

The quantity of carbohydrate and protein destroyed by decomposition in the stomach, and thus wasted as far as nutrition is concerned, is so small in proportion to the total food consumed that it is practically of no importance. It is only indirectly, by upsetting gastric and intestinal digestion, that decomposition exerts any influence upon general nutrition.

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II.—DISEASES OF THE INTESTINE.

INTRODUCTION.

The rôle of the intestine is to complete the digestion of foodstuffs begun by the stomach, to absorb the products of this digestion, and to evacuate *per anum* the indigestible residue, together with certain other excretory substances. Although these functions are very manifold, we can divide them into secretory, motor, resorptive, and excretory. Certain processes of decomposition occur coincidently, even under normal conditions. In this respect the intestine differs from all the other hollow viscera. The two main portions of the intestine, the small and the large, take part in unequal degrees in the various functions. The secretory rôle falls almost entirely to the share of the small intestine and of the large digestive glands, the liver and pancreas, which pour their secretion into it. The secretory products of the latter organs may be considered along with those of the bowel. Resorption for the most part also takes place in the small intestine. The colon absorbs water with avidity, but no fat at all, and only small quantities of carbohydrate and protein. It therefore follows that the colon plays almost a passive part in digestion. It is a large reservoir, in which the fermentation changes, begun but not

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completed in the small intestine, are consummated. This process, however, is restricted to the upper portion of the colon, in which the chyme makes the longest stay, the latter being about fourteen hours according to Sicard and Infroit (1). It appears that the lower portion of the large intestine is the chief site of excretion of salts, fats, and foreign substances. Both the small intestine and the bile have a similar excretory function, but to a much less degree. Lastly, processes of decomposition barely commence in the small intestine; these and the fermentation of carbohydrate are almost limited to the lower portion of the colon. The ileocæcal valve forms a sharp line of demarcation.

The close interrelationship between the various functions makes it particularly difficult to follow and to understand the disorders of intestinal digestion. It is clear that disturbance of secretion must bring in its train a disturbance of absorption. The same is true of increased peristalsis. Disorders of secretion, as well as those of resorption, can in their turn lead to increased peristalsis, by allowing further decomposition of the contents, and so on. In addition, there are in the intestines several secretions for each group of food-stuffs: gastric and pancreatic juices for protein; bile and pancreatic juice for fat; saliva, pancreatic juice, and succus entericus for carbohydrate. The conditions are much simpler in the stomach. Our methods for determining the total quantities of the several intestinal secretions, and for measuring the motility of individual portions of the bowel, are still very imperfect; indeed, almost all our knowledge of them has been acquired from pathological cases. In the case of the stomach we were able to classify the disorders under the headings of the separate gastric functions. It is easy to understand that a similar classification in the case of the intestine can only be an incomplete one. Nevertheless, an attempt at such a classification will be made in the sections which follow.

A.—DISORDERS OF SECRETION.

1. Disorders of Bile Secretion.

Just as in the case of the secretion of gastric juice, so here an increased and a diminished or absent secretion of bile may be recognised. The first, termed "pleiocholia," or, if only the bile pigment be increased, "pleiochromia," is a result of blood destruction. It will be discussed more fully in the chapter upon Diseases of the Liver. It causes no serious disturbance in the intestine. The second, termed "hypocholia" or "acholia," as the case may be, is most commonly the result of biliary obstruction. The consequences for the intestine are considerable; but usually they only become obvious when the stagnation of the bile is so great that bile pigment enters the blood and causes jaundice. It is very probable that even the slighter changes in bile secretion or bile formation, which stop short of jaundice, do produce disorders of the bowel; but the fact has not yet been definitely proved. Nothnagel (2) formerly believed

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that the so-called *acholischen Stühle ohne Ikterus* must depend upon a temporary and functional cessation of bile secretion. Later (3) he accepted the view of von Jaksch (4) and Fleischer (5) that the cause of the phenomenon is either an imperfect resorption of fat from the bowel, or else an excessive reduction of the bilirubin itself to urobilinogen. In England it is common to attribute various indefinite digestive disturbances, such as varying colour of the fæces, feelings of oppression and fullness over the liver, dirty yellow discoloration of the conjunctiva and skin, general sensations of being out of sorts, to variations in the bile-forming activity of the liver, or "biliousness" (6). No exact researches have been carried out upon this question.

(*a*) *Influence of Stagnation of the Bile upon Intestinal Digestion.*

Complete stagnation of the bile reacts upon the secretion of gastric juice, and leads to its increase. Von Noorden (7), Riegel (8), and recently Simnitzky, (9) find hyperacidity in cases of obstructive jaundice, whatever the cause. I have repeatedly found the same. Von Jaksch (10) alone records diminished secretion of hydrochloric acid in some cases of catarrhal jaundice. It is not known whether or not there is any change in other secretions, such as the pancreatic juice and the succus entericus.

Stagnation of bile is also said to affect the motor activity of the bowel, diminishing it. The view that jaundice causes constipation is very generally held. The experimental grounds for the belief, however, are very scanty [Schülein (11)]. Clinical observations, made with special care [Boas (12), Schmidt (13)], teach the exact reverse—namely, that the motions, in cases of complete absence of bile, may be copious and strikingly loose. In consequence of the imperfect resorption of fat one would expect that the fæces should be soft, and three times their usual bulk (*vide infra*).

Besides this, it is probable that the colon is mildly stimulated by the free fatty acids, which are present in considerable amount.

The Influence of Bile Stagnation upon Resorption in the Intestine.—F. Müller (15) measured the amount of ingesta and the residue lost *per anum*, and compared the two in patients with jaundice in whom there was more or less obstruction to the flow of bile into the duodenum. The following summary of his results agrees essentially with those obtained by experiments on animals with biliary fistulæ.

1. In no case was there much interference with the assimilation of carbohydrate.

2. The assimilation of protein was approximately the same as in health. Very often it was slightly diminished, but in such cases the impairment was secondary, and due to the bulk of fat not absorbed. It is a frequent thing for deficient assimilation of one class of food-stuff to interfere to a small extent with that of another [F. Müller (16)].

3. The assimilation of inorganic matter was normal, and in two cases better than in health.

4. The resorption of fat was greatly impaired, and quite as much so

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upon milk diet as upon one of meat, wheaten bread, and butter. The following table of Müller's illustrates this point:

No.	*Subject.*	*Food.*	*Fat in Food per Day.*	*Loss in Fæces.*
			Gm.	Per Cent.
1	Healthy	Milk	69·1	7·2
2	,,	Milk	94·2	6·9
3	,,	Milk and white bread	65·9	10·5 (Average loss 8·2)
4	Jaundiced	Milk and white bread	78·4	63·5
5	,,	Milk and white bread	85·1	74·1
5	,,	Meat, white bread, and butter	39·5	78·5
6	,,	Milk, white bread	54·4	39·5
6	,,	Meat, white bread, and butter	26·6	31·5
7	,,	Milk	35·3	66·9
7	,,	Milk and white bread	52·6	55·2 (Average loss 58·5)

Müller's results have been confirmed by everyone who has repeated his experiments. The only point upon which opinions differ is in regard to the amount of fat lost. My own observations (17), which were all made when the diet was fixed as to both quality and quantity, showed an average fat loss of only 25·9 per cent. upon a daily intake of 83·4 grammes of fat in the form of milk and butter. The following are my figures:

Subject.	*Fat in the Dried Fæces.*	*Absolute Fat Output per Three Days.*	*Unabsorbed Food Fat.*	*Decomposed Fat in Fæces.*
	Per Cent.	Gm.	Per Cent.	Per Cent.
Healthy	21·45	12·93	5·17	60·29
,, ...	21·93	13·60	5·43	64·31
,, ...	26·61	14·80	5·91	56·89
Average	23·24	13·78	5·50	60·50
Biliary obstruction	48·48	57·13	22·79	67·06
,, ,,	43·87	69·31	27·70	46·45
,, ,,	53·59	68·06	27·20	85·00
Average	48·65	64·83	25·89	66·84

In two of the patients there was complete obstruction to the bile passages. Albu (18) has observed a similarly small loss in a case of chronic biliary obstruction. It seems likely that differences in the food taken or variations in the degree of the vicarious function possessed by the other digestive juices may account for these discrepancies.

The fæces, in cases of biliary obstruction, assume the characteristic appearance of *fatty stools*. Their amount, provided the diet remain the same, rises to three or four times the normal (19). The proportion of water is not altered. The specific gravity falls below 1000, so that the

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fæcal material floats on water. The reaction becomes strongly acid owing to the presence of free fatty acids. To the naked eye the stool which is deficient in or entirely lacks bile, appears greyish-white, scintillating on the surface. Its consistence is that of soft putty. Microscopical examination shows the greater part of the fæces to consist of fine needle-shaped crystals [C. Gerhardt (20)], of which only a few melt into droplets on warming the slide. The majority melt only after the preparation has been acidified. This indicates that they consist of saponified fats. Chemical analysis [Oesterlein, Fr. Müller, Stadelmann, Kimura (21)] confirms this. By far the greater part consists of the calcium salts, not the magnesium salts as Oesterlein thought, of the higher fatty acids—palmitic and stearic.

Corresponding to these micro-chemical observations are the results of extracting the fæces with ether. F. Müller has shown that about three-fourths of the total fats are present as fatty acids or soaps, and only one-quarter as neutral fat; that is to say, that in biliary obstruction the splitting up of the fats takes place to the same extent as under normal conditions—namely, up to about 75 per cent., or, according to my own figures, up to 66·8 and 60·5 per cent. of all the fat present. Müller has proved, further, that the melting-point of the fat in the fæces in cases of biliary obstruction is no higher than that of the fat in the food, but that the melting-points of the two are approximately the same.

To sum up, the effect of biliary stagnation upon food resorption consists almost entirely in the impairment of the digestion of fats. This impairment is not lessened by giving the fat in an emulsified form, such as milk. The chief function of the bile is thus not so much one of emulsifying the fats as of rendering the fatty acids and soaps soluble, and of stimulating the epithelial cells of the intestinal mucosa to absorb them.

The question of what is the effect of biliary stagnation upon decomposition in the alimentary canal is one which has been much debated, and has not yet been settled. It has been proved that the bile itself has practically no antiseptic properties. It does not hinder the growth of micro-organisms in culture media (22). It often becomes itself infected in the gall bladder. It is true that bile acids, when they are free, are slightly antiseptic. This makes the question a little more complicated, for Macfadyen (25) showed that an acid reaction of the intestinal contents had an inhibitory effect upon the putrefaction of protein. It does not follow, however, that this is due to the antifermentative action of the bile acids.

It by no means follows that the results found *in vitro* can be at once assumed to be true of the conditions in the living bowel. It is true that the hydrochloric acid from the stomach and the organic acids produced in the contents of the intestine would tend to liberate the bile acids from their alkaline salts, but it is not known how quickly the basic avidity of these bile acids will cause them to recombine with alkalis again. The acidity of the intestinal contents is due much more to other organic acids than it is to bile acids. Moreover, it seems likely that the presence of protein and peptone suffices to reduce the antifermentative power of bile acids to a minimum, as they do that of corrosive sublimate [von Noorden (7)].

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Careful clinical observations may throw some light upon the question. Numerous researches have already been made upon the intensity of protein putrefaction in the bowel in cases of jaundice from biliary obstruction. All observers have used Baumann's method—namely, that of estimating the ethyl-sulphuric acids in the urine. The results obtained have been contradictory. On the one hand, Brieger, Müller, Biernatzki, Eiger, Schmidt, and more recently Böhm, found the figures high; on the other hand, Röhmann, Müller, Pott, von Noorden, Stern, Hirschler, and Terray (27) found them normal or even diminished. This contradiction is not to be wondered at when it is remembered that all these observers estimated only the putrefaction products in the urine, and most of them only those that were present as ethyl-sulphuric acid. It is only the sum total of the putrefaction products present in the urine and fæces together that can yield any real measure of the decomposition of protein (see discussion on p. 172). This method of investigation is unsatisfactory, and better methods are necessary before any advance can be made.

Bidder and Schmidt (28) maintain that the fatty stools of jaundice have a particularly foul odour. Closer investigation makes this fundamental point somewhat doubtful. Even if unpleasant, the smell of the fæces in cases of uncomplicated biliary obstruction is by no means stinking, like that of stools that are really decomposing [A. Schmidt (29), Albu (18)]. Brieger holds that aromatic bodies of unknown composition are present. I myself believe the higher fatty acids to be responsible for the smell. If one applies my incubation test (30) to these fatty stools, one finds their disposition to putrefy to be very slight. They do not ferment even when starch is added to them, neither do they putrefy, provided the pancreas and the intestine are healthy. Fatty stools have an acid reaction owing to the presence of fatty acids. One may speak, perhaps, of a fat decomposition or rancidity in the fatty stools of jaundice, but not of protein putrefaction.

These conclusions are confirmed by the researches of Strasburger (31), who determines the total bulk of bacteria in the fæces, and finds a remarkable diminution in the fæcal bacteria in cases of jaundice. This is exactly the reverse of what would be expected were the prevalent view accepted.

There is no ground whatever for the teaching that absence of bile causes increased intestinal decomposition. Indeed, if this were so, it would be remarkable that complete biliary obstruction, lasting over several months, never leads to catarrh and enteritis provided no complications supervene.

(*b*) *Influence of Bile Stagnation upon other Organs and upon Metabolism.*

See the chapter upon Diseases of the Liver.

(*c*) *Influence of Bile Stagnation upon General Nutrition.*

There have been no experiments carried out upon either the heat-production or the oxygen requirements of people with jaundice; never-

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theless, no figures are needed to demonstrate their increase or diminution. Even if the metabolism of oxidizable material remains unchanged, nutrition may suffer in every case of jaundice, and it generally does suffer. The weights of patients prove it conclusively. The reason is to be found in the poor resorption of fat. Hence such patients utilize little fat. Without increasing the volume of food it is difficult to produce the necessary number of calories if fat is not included in the diet. In some forms of jaundice large quantities of food cannot be given because the appetite is poor, and gastric pain follows a big meal. This is the case, for example, in catarrhal jaundice, and particularly in patients who have gall-stones [J. Kraus (32)]. Theoretically, it should be possible to maintain the nutrition of patients by giving larger quantities of albuminates and carbohydrates when bile is prevented from entering the intestine. Voit (33) and Winterer (34) have shown it to be possible in dogs with biliary fistulæ. In most cases, however, this is impossible in man, and the patient uses up part of his own body fat—or fat and protein —to supply some of the calories he requires [von Noorden (71)].

2. Disorders of the Secretion of Pancreatic Juice.

(a) *Influence of Deficiency of Pancreatic Juice upon Intestinal Digestion.*

The only disorder of the secretion of pancreatic juice that is of practical importance in digestion is its complete absence over a long period. This may arise from obstruction to the pancreatic duct, or from degeneration of the parenchyma of the gland. Temporary cessation, diminution, or increase of pancreatic secretion cannot yet be diagnosed, although it is probable that these conditions do occur. Even with complete absence of pancreatic juice there need be no disturbance of digestion (35). It is not clear how the adjustment is made; possibly it depends on many factors, such as the almost constant presence of two ducts to the gland, the occurrence of accessory pancreatic tissue, the far-reaching compensatory action of minute gland-rests which are known to ward off the onset of diabetes in many cases, and the vicarious action of other digestive juices. Amongst the latter may be mentioned fat-splitting by gastric juice and putrefaction in the intestine, protein digestion by gastric juice and (?) by succus entericus. Finally, a possibility which has yet to be proved must not be forgotten—the ferments may perhaps reach the bowel through the circulation when the gland-ducts are blocked.

Nothing is known about any influence that the absence of pancreatic juice exerts upon the *secretion of other digestive juices*, nor can anything be said concerning motor disorders resulting from deficiency of pancreatic juice. Still, diarrhœa readily sets in when much food residue remains and decomposes in the bowel. This can hardly be regarded as other than a very indirect result of the deficiency of pancreatic juice.

The chief effect of such deficiency is a considerable impairment of resorption from the intestine. This affects particularly the fats and the

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proteins. That the carbohydrates are absorbed at the normal rate and extent will be evident from a reference to the experimental data given under references 36 to 51 inclusive.

Diminished fat resorption is evidenced by the fatty stool. This at first sight resembles that of biliary obstruction. It often happens that both pancreatic and bile ducts are obstructed simultaneously owing to the close proximity of their openings into the duodenum. When the pancreatic duct alone is obstructed the fatty stool differs from that of biliary obstruction in the following respects :

1. It still contains bile pigments.

2. Fatty acids and soaps do not constitute so large a percentage of the fat present ; a large part of the latter is still neutral fat. On microscopical examination fine droplets are seen. These dissolve in ether, stain black with osmic acid, and red with Sudan III. In marked cases the presence of neutral fat may be recognised by the naked eye. The newly-evacuated fæces are covered with a film of fluid fat which rapidly congeals on exposure.

3. Remnants of muscle are present, and may sometimes be recognised microscopically.

4. In consequence of (3), there is a greater liability to putrefaction either in the air or in the incubator.

Chemical analysis affords us a still deeper insight into the mechanism of the above disorders. In comparison with the loss of fat that occurs when there is deficient bile, the percentage associated with deficient pancreatic secretion is less constant, and often remarkably small. The figures show very wide variations. F. Müller (45) found no increase of fat in the fæces. Among later observers, on the other hand, Deucher (46) observed 52·6 and 83 per cent. of fat loss, whilst Oser (42) and Pribram (52) obtained similar figures. Midway between these extremes come the results of Weintraud (48), who found 22·2 and 25·2 per cent. of fat loss. The results of animal experiments show comparative agreement with these clinical observations. They indicate, almost without exception, that fat resorption is very markedly impaired after complete extirpation of the pancreas, quite as markedly as with biliary obstruction.

How are these different observations to be reconciled with one another ? To answer this question a fact mentioned at the beginning of this section may be recalled. This is, that even complete absence of pancreatic juice need not necessarily lead to digestive disturbances. In human pathology it is often extremely difficult, or even impossible, to say that there are no gland-rests able to carry on a particular function, or that when one duct is closed secretion cannot still reach the bowel through a second duct or from accessory glands. This is especially true for both of F. Müller's cases, as Abelmann points out. In animal experiments the extent of a given lesion can be controlled, although it must be remembered that total extirpation of the pancreas is a very severe operation, which may easily upset the bile secretion also [Krehl (53)]. Sandmeyer's and Rosenberg's experiments show clearly that simple closure of the duct, leaving the small gland-rests behind, causes disturbances of resorption, which ensue slowly, and are slight in comparison to those produced

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by total extirpation.[1] In this connection the form in which the fat is administered in the food is important.

Abelmann's (37) dogs, after extirpation of the pancreas, excreted in the fæces almost all the fat administered without previous emulsification. On a milk diet they lost only 43 to 70 per cent. According to this the fat is better digested when it is given in natural emulsion. There are no records upon this point in man. Should it be confirmed, there must be a remarkable difference between the results in pancreatic and in biliary obstruction, for with the latter, as has been mentioned, the giving of emulsified fat in the food does not diminish the percentage of fat lost.

As regards the quantity of neutral fat in the pancreatic fatty stool, chemical analyses are again widely at variance. F. Müller (15) has propounded the view that, when pancreatic secretion is out of order, it is the splitting up of the fat in the intestine which essentially suffers. He bases this belief on his two clinical cases, in which only one-third to one-fifth of the fat in the fæces had been split up, instead of three-quarters, as under normal conditions or with biliary obstruction. His view receives additional support from further striking observations made by von Noorden (45), Anschütz (56), and Weintraud (48). Quite recently Katz (49) has strenuously upheld the same doctrine. He carried out a number of researches upon the fæces of patients known to have some interference with the flow of pancreatic juice. He believes it possible to conclude that there is a pancreatic lesion whenever less than 70 per cent. of the fats are split up, the exceptions being infants at the breast and patients suffering from profuse diarrhœa. Katz further adds that the decrease in the fats split up is greater when the interference with the pancreatic juice is acute than when it is of slow onset.

In opposition to these views are Deucher's (46) results. He investigated two incontestable cases of severe affection of the pancreas. He found the splitting up of fats in the intestine to be as complete as it is in healthy people, or in those who have other affections of the bowel. His figures show 80 and 62 per cent. of the fat to have been split up. Albu (18) supports this by a case in which he found 80 to 90 per cent. of split-up fat. All these figures agree uncommonly well with the results obtained in animals by Abelmann and others. According to all it is essential that the fat in the food should be well emulsified if it is to be properly split up in the absence of pancreatic juice. When the emulsion is fine, the gastric juice can to some extent act as a substitute for the pancreatic juice [Volhard (54)]. In any case, there is no necessity to suppose that the intestinal bacteria have a fat-splitting action [Hédon and Ville (43), Rosenberg (41)]. Müller has pointed out that even if the bacteria had such an action, it could but poorly replace the fat-splitting ferment of the pancreas.

Compared to the relation of the neutral fats to the fats which have been split up into fatty acids and soaps, that of the free fatty acids and the soaps to one another is without significance. According to Müller it is fortuitous, depending on the amount of alkali that happens to be present at the place where the fat is split up. Zoja (50), however, thinks that if

[1] This has been confirmed by E. Zuntz and Meyer (*D. med. W.*, 1904, No. 41).

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the amount of soaps is small, it is as important an indication of defective pancreatic secretion as is a large quantity of neutral fat. He quotes in his favour the figures found by Deucher (46)—7 to 9 per cent. of soaps, against 42 to 45 per cent. in health.

Brugsch (*Z. f. Klin. Med.*, 1906) states, from the examination of a number of cases, that while any excess of fat above 30 per cent. points to faulty absorption, it is not safe to diagnose disease of the pancreas solely from the percentage of fat in the stools. Faulty cleavage of fat does not alone indicate pancreas disease.

Yet another observation of Deucher's led him to affirm that the quantity of lecithin in the fæces is a measure of the deficiency of pancreatic juice. Normally only traces of lecithin are found in fæces. Deucher found up to nearly 8 grammes per diem in cases of pancreatic disease. When it is remembered that lecithin is probably broken up by pancreatic digestion into glycero-phosphoric acid, neurin, and fatty acids (55), it is easy to understand Deucher's theory that lecithin will be in excess in the fæces when pancreatic secretion is impaired. More observations on this point are much needed.

We now pass on to the impairment of protein digestion, which results from deficient activity of the pancreas. It manifests itself clinically by the reappearance in the motion of numerous particles of meat remnants, especially muscle fibres (35). These may usually be detected by the naked eye. The same thing is expressed chemically by the raised nitrogen contents of the fæces. This has been termed "azotorrhœa." Hirschfeld (47), in pancreatic diabetes, recovered from the fæces 32 per cent. of the nitrogen given by the mouth. Zoja (50) and H. Salomon (57) recovered as much as 70 per cent., an amount which comes very near that found in experiments upon animals (36, 37, 41). Weintraud (48), whose corresponding figures in a case of probable pancreatic disease were 42 to 46 per cent. discusses the diagnostic significance of this azotorrhœa. He says that in affections of the pancreas the protein resorption is more, or at least not less, affected than is that of fat, whereas in diseases of the intestine, such as ulcerations or lardaceous disease, it is not interfered with so much.

As a matter of fact, the combination of azotorrhœa and steatorrhœa might be used as a means of diagnosing disorders of the pancreas. Unfortunately the process of quantitative analysis of the fæces is too complicated for clinical use. At the same time Weintraud's statement is based upon far too small a number of cases. Brugsch (*Z. f. Klin. Med.*, 1906) finds that in diseases of the pancreas the loss is 20 to 25 per cent. of the nitrogen intake, and 50 to 60 per cent. fat. When the bile duct is obstructed alone the loss is 11 per cent. nitrogen, and 45 per cent. fat; when both the bile and pancreatic juice are absent, there is 33 per cent. of the ingested nitrogen and 50 to 90 per cent. of the ingested fat in the fæces.

Sahli (58) uses another method of investigating pancreatic activity. He gives what he called "glutoid capsules." These are gelatin capsules, hardened in formalin, and rendered difficult of digestion. They are said to resist the action of gastric juice, but not that of the pancreatic secretion.

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When they contain iodoform, it can only be absorbed from the alimentary canal when the pancreas is pouring out plenty of active juice. Unfortunately this ingenious test has not been successful in clinical practice (59).

Another diagnostic test has been suggested by myself (60). It may in the future be found to apply when pancreatic secretion is in complete abeyance. It consists in the finding of persistent nuclei in the muscle fibre fragments excreted with the fæces. Pancreatic juice is the only secretion in the alimentary tract that has the power to digest nuclear substance. Putrefaction in the bowel can by itself destroy the nuclei of fresh tissues only when it is very active, and when it acts continuously for thirty hours. On this I have based a clinical method, which consists in administering, along with a test meal, some small pieces of meat enclosed in minute flasks. Some remarkable results have been obtained already.

Salomon (57) has recommended another method. He administers pancreatic substance in the form of "pancreon." If the symptoms of azotorrhœa and steatorrhœa disappear or decrease, there is ground for suspecting some affection of the pancreas. Even if this gives no absolute means of differentiating pancreatic from other severe disorders of resorption, it at least affords very serviceable assistance.

A few words are necessary in regard to the digestion of carbohydrates in disorders of the pancreas. According to F. Müller (15) and other authors it is not interfered with at all. I must mention, however, that I have lately found a positive result with the fermentation test in several cases of pancreatic fatty stools; this I am unable to pass over in view of Pribram's (52) negative results. Rosenberg (41) also found some impairment of carbohydrate assimilation in experiments upon animals.

The literature contains contradictory statements as to the effect defects of pancreatic secretion have upon decomposition in the alimentary canal. Gerhardi (63) and Pisenti (64) found considerable diminution of the indican in the urine; on the other hand, Oser and Katz (65), in animals, found an increase in both the indican and the ethyl-sulphuric acid. I myself have already pointed out that the presence of muscle remnants in the pancreatic fatty stool render it particularly liable to putrefy. I did my experiments in the incubator, and I find I am supported by an observation of Abelmann's (37) in a dog whose pancreas had been extirpated. He says that "the usual penetrating odour of the meat-containing fæces was present, and the urine showed the presence of combined sulphuric acid." It is therefore impossible to speak of diminished intestinal putrefaction as a phenomenon of deficient pancreatic secretion; rather is the reverse the case.

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(*b*) *Influence of Disorders of Pancreatic Secretion upon other Organs and upon Metabolism.*

One of the commonest results of pancreatic disease is the appearance of sugar in the urine—*pancreatic diabetes*. It probably depends not so much upon disorders of the secretion of pancreatic juice as upon defects of an internal secretion of the gland. Glycosuria, pentosuria, lipuria, and acetonuria are discussed in an earlier chapter.

According to Jablonsky (66), the urine of dogs with pancreatic fistulæ is much more acid than normal. This is due to the drain of alkali from the blood, owing to the loss of alkali in the pancreatic juice. Other observers (67) noticed that, in addition to glycosuria, extirpation of the pancreas leads to polyuria, azoturia, and increased excretion of phosphates. There are no publications upon this point in human pathology.

Bronzing of the skin occasionally occurs in pancreatic diabetes. In very rare cases it has been seen without glycosuria when the pancreas has been diseased (68).

No causal connection has hitherto been shown to exist between disturbances of pancreatic secretion and the excessive flow of saliva that is now and then seen.

The phenomenon of multiple fat necrosis may now be considered. This is beyond doubt closely related to diseases of the pancreas, especially to disorders of its secretion. It is by no means uncommon. Balser and Chiari regarded the process as a simple degeneration, a necrosis of the fat cells (69, 70). Langerhans, by the aid of micro-chemical reactions, concluded that "multiple necrosis of adipose tissue begins with a splitting up of the neutral fat contained in the cells; the fluid constituents are eliminated, and the more solid fatty acids remain behind. These combine with calcium to form their calcium salts. The whole fat lobule, or several adjacent lobules, then forms a dead mass, which becomes separated from the living tissues by inflammatory reaction around it" (70).

Langerhans only suspected the actual cause of fat necrosis. Hildebrand, in 1895, from experiments on animals, was led to ascribe the condition to the action of steapsin—the fat-splitting ferment of the pancreas—upon the abdominal fat. In contrast to this, Ponfick, like Balser, thought fat necrosis must be regarded as a genuine idiopathic disease, probably of micro-parasitic origin. Of the two theories, that of the pancreatic ferment has lately received support from the experiments of Körtes and the critical observations of Truhart. It is now generally allowed that the fat-splitting ferment of the pancreas is the active factor in the etiology of fat necrosis. The steapsin must reach the adipose tissue directly from the gland, and not first pass into the blood. It follows from this that fat necrosis chiefly occurs after injury to, or rupture of, the pancreas, and particularly in hæmorrhagic pancreatitis, in which the parenchymatous cells are themselves diseased. In these conditions the products of secretion find their way directly into the neighbouring tissues. Truhart supposes that the trypsin, by its power of dissolving protein, makes a path for the steapsin to follow. Katz and Winkler

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think that the leucocytosis which so often accompanies fat necrosis is due to absorption of the secretory products into the blood (70).

(c) *Influence of Disorders of Pancreatic Secretion upon General Nutrition.*

Long-standing and complete absence of pancreatic juice leads to inanition and death. This is the case whether diabetes ensues or not. Nutriment drains away into the fæces unused. It is possible to check this temporarily by artificial feeding with fresh pancreas. No exact figures upon the duration of life are to hand. In experiments upon animals diabetes is an unavoidable complication. In human pathology, as in cases of pancreatic calculus, cysts, and cancer, the secretion is not stopped all at once, but usually by degrees. Clinically, the emaciation is generally gradual, but progressive to an extreme degree. At the same time, it is remarkable how small is the minimum quantity of food that will keep these emaciated patients alive—a point already mentioned in connection with pyloric stenosis. It is also remarkable how long the body can accommodate itself to a diminished supply of pancreatic juice. There are often no symptoms whatever until long after the disease has begun.

3. Disorders of the Secretion of Succus Entericus.

The most recent researches upon succcus entericus [Cohnheim, Glassner, Hamburger, and Hekma (71)] ascribe a far greater importance to this secretion than it has up till now been generally supposed to possess. They have shown that succus entericus contains a body, termed "enterokinase" by Oppenheimer. This renders trypsin active, and is therefore of great importance in the digestion of protein. Casein can apparently be dissolved by succus entericus by itself. The fat-splitting action of pancreatic juice is made stronger by it. There is in succus entericus an amylolytic ferment which is potent in inverting cane-sugar and in converting maltose into dextrose. Pancreatic juice cannot thus act upon maltose.

This being so, it might be expected that disturbances of the intestinal secretion, which certainly occur, would lead to digestive disturbances that could be readily recognised, affecting carbohydrates mainly, and protein in less degree. Unfortunately, the conditions are, as yet, but little known, and, as a rule, they are much mixed up with other disorders of secretion, such as those of the gastric and pancreatic juices and of the bile.

Nevertheless, one disorder in which the succus entericus is alone at fault can be fairly well distinguished. This is the clinical picture to which Schmidt and Strasburger (72) have given the name "intestina. fermentation dyspepsia." In their cases the symptoms were mainly subjective, and consisted in obscure pains and fluttering sensations in the abdomen, diminished appetite, and general feelings of being out of sorts. Objectively, the patients looked fairly well, except that there were slight fullness and hyperæsthesia of the abdomen, a coated tongue, and some-

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what increased frequency of defæcation. The fæces were usually frothy, bright yellow, and acid; on incubation, they showed marked carbohydrate fermentation. Corresponding with this, chemical analysis showed that twice as much carbohydrate was present as in normal fæces; the nitrogen excretion was not appreciably increased, and the fat was normal. Mucus was never present. The functions of the stomach were natural. These clinical signs agree exactly with the disturbances one would expect theoretically. Schmidt and Strasburger considered that the affection must be regarded as a slight, almost functional, hypo-secretion.

In contradistinction to these depressor disorders, one would expect excitatory affections to occur also of the nature of hypersecretion of the succus entericus. Such are not known. It would serve no useful purpose to regard as such the so-called nervous diarrhœas, nor those rare cases of enterorrhœa (73) in which a watery fluid, containing digestive ferments, is periodically discharged *per anum*. In the same way, it cannot definitely be said that there is any relation between disturbances in the secretion of succus entericus and those cases which Nothnagel (74) has described under the name of "jejunal diarrhœa." In all these there are other disorders as well; the secretion of the pancreas and the motility of the bowel are concerned as much as is the succus entericus [Schmidt (75)].

Pathological conditions arising from variations in the output, etc., of erepsin and secretins have not yet been sufficiently investigated. In some cases, Moore, Edie, and Abram (*Bioch. Journal*, 1906) have obtained an improved action of the pancreas after administration of secretin. Bainbridge and Beddard (*ibid.*) report opposite results.

B.—MOTOR DISORDERS.

The known motor disorders of the bowel may be classified as follows:

(1) Increased or diminished peristalsis; (2) complete paralysis or spasm of the intestine; (3) stenosis or occlusion of the lumen of the bowel.

Whereas the last two are rarely observed, increased and diminished peristalsis are of daily occurrence. In the minds of many physicians and of all the laity they are synonymous with diarrhœa and constipation. This, however, is wrong. The two conditions which constitute diarrhœa are too frequent evacuation and too thin a consistency of the fæces. These can to a certain extent be independent of each other. The converse is true of constipation. Both conditions owe their occurrence almost entirely to the large intestine. Of the motor disturbances of the small intestine little is known, so far as increased and diminished motility are concerned. There are very wide variations in the etiology of diarrhœa and constipation. Without fully considering the question, it may be mentioned that very few disorders are dependent primarily upon changes in the motility of the intestine, and that, as yet, it is difficult to sharply delineate them. It is therefore impossible to give a clear outline of any special disturbances of metabolism which result from changes in intestinal motility.

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1. Influence of Motor Disorders upon Intestinal Digestion.

It seems likely that motor disorders of the intestine would affect the secretion of digestive juices; Wiczkowski (77) associates diarrhœa with diminished secretion of hydrochloric acid in the stomach, constipation with the reverse. Ebstein (78), on the other hand, maintains strongly that in the cases of chronic and habitual constipation he investigated, the hydrochloric acid and the digestive power of the stomach were normal. My own view is that intestinal motility is so often affected secondarily to a primary secretory disturbance in the stomach that the occurrence of the two always lead me to consider the gastric condition as the cause, the intestinal as the effect. This question is discussed in the earlier part of the present chapter.

It is certain that resorption in the bowel is affected by disturbances of motility. This is shown by the different proportions of water the fæces contain in diarrhœa and in constipation. Nevertheless, the action of peristalsis upon the amount of resorption has been much overestimated.

Diarrhœa, as has been mentioned, is often due simply to overactivity of the colon. The large intestine has only a small share in the resorption of food-stuffs (79). It takes up large quantities of water. Its overactivity, therefore, leads to the passage of watery motions containing little undigested residue of food. Even in the cases in which the lower part of the small intestine is also affected the food residue need not be great. In this connection von Hösslin's (80) researches upon food assimilation in typhoid fever are interesting. In typhoid fever, and in other ulcerative conditions, diarrhœa often arises simply from irritation of the bases of the ulcers, without there being any disease of the intervening mucous membrane (81). In those cases of diarrhœa in which a superficial affection of the mucosa of the small intestine is the cause—namely, catarrh, toxic processes, cholera, uræmia, and so on—it is common to find very defective assimilation. In these cases the resorptive power of the mucosa and the secretory function are affected at the same time as the motility.

It is of little use to give exact figures when the question is so complicated. The reader may refer for fuller details to Schmidt and Strasburger's (82) works. The unassimilated food consists of protein [Schmidt] and carbohydrate [Strasburger (84)], as well as fat, even in the slighter degrees of diarrhœa. In severer cases the motion further contains protein in solution, and diastatic and proteolytic ferments (85) in such amounts as to be easily demonstrable.

It has hitherto been held that chronic and habitual constipation leads to concentration of the fæces entirely through increased resorption of water. Lohrisch (86) has recently brought evidence to show that there is increased resorption of all kinds of food-stuffs in this affection. He bases his belief upon some observations made by Schmidt and Strasburger. It cannot be assumed, however, that the slowing of the movements of the colon improves assimilation. It is much more likely that good assimilation of the food is the primary condition.

In cases of occlusion or extreme stenosis of the bowel resorption of

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nutriment is much impaired. This is also the case in intestinal paralysis, which acts very much as does stenosis. The impairment is partly due to venous stagnation in the intestinal wall, partly to decomposition of the contents and resultant inflammatory changes.

Our views upon the influence of disorders of bowel motility upon decomposition of the contents have recently undergone considerable change. Formerly, the only way of measuring such decomposition was by estimating the products of putrefaction and fermentation that were excreted in the urine—namely, indican, ethyl-sulphuric acid, aromatic oxy-acids, and volatile fatty acids. As long as this was so the universal belief was that, with a few exceptions, constipation was associated with increased, diarrhœa with decreased, decomposition (87). Since attention has been paid to the same kind of substances in the fæces [Baumstarck, Ury (88)], it has been proved that the amount of resorption is of very great importance. The fæces are rich in products of decomposition when the urine is poor, and *vice versa*. The careful work published by Ury will elucidate the whole question in the near future. It already seems clear that simple decrease and increase of peristalsis—at least, as far as the colon is concerned—have little or no influence upon the amount of decomposition. The latter is augmented when large quantities of material liable to decompose—mucus and other inflammatory products, soluble protein, and so on—are present at the same time; or when the small intestine is simultaneously affected, owing to incompetence of the ileo-cæcal valve, stenosis, or other similar conditions. Indeed, Strasburger (89) maintains that the total number of bacteria in the fæces is less in constipation than in diarrhœa.

2. Influence of Motor Disorders upon other Metabolic Processes, and upon General Nutrition.

Besides the toxic effects, or auto-intoxications, which are caused by the formation of various products of putrefaction, and of which we shall speak again, motor disorders of the bowel may, under certain conditions, produce marked changes in the amount of water in the tissues. Very severe diarrhœa, such as that of cholera, leads to anuria, and to such dehydration of the skin that a fold of the latter picked up between the fingers takes quite a long time to go down flat again. This dehydration does not in itself appear to be dangerous. The nephritis of cholera is no longer attributed to it, but to the action of toxines. The same is true of tetany, which is far less commonly seen with diarrhœa than it is with pyloric stenosis.

It is obvious that general nutrition must suffer in severe diarrhœa. In many cases, however, the effect is but slight. This is particularly so if the increased peristalsis occurs only in the colon or in the upper part of the small intestine, leaving time enough for resorption in the lower portions. In chronic habitual constipation, on the other hand, we frequently see a tendency to corpulence, corresponding to the increased assimilative power of the mucous membrane.

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C.—DISORDERS OF ABSORPTION.

Altered absorption is present in most affections of the intestine, and being frequently the only sign of intestinal disorder, it serves as a starting-point for diagnosis. This is particularly so in secretory disorders, though it is also the case in certain motor disturbances. Amongst the latter may be mentioned diarrhœa due to the inflammation of the mucous membrane, as a result of which every function of the intestine is usually upset.

Even in cases where intestinal resorption is commonly regarded as primary it is not unusual to find a certain amount of inflammatory change, or even ulceration. It is therefore only with a certain degree of reserve that the symptoms can be described as entirely dependent upon impairment of the power of resorption; for example, in venous engorgements from heart failure or cirrhosis of the liver, in lardaceous disease of the intestine, and in tuberculous caseation of the mesenteric lymph glands. Nevertheless, it is mainly from cases like these that the relation between resorptive power and metabolism can be judged.

Those cases of functional resorptive disturbance [Salomon, Schmidt (90)] in which, under certain circumstances, the assimilation of only one of the groups of food-stuffs, such as fat or protein, may be interfered with may also be included. Intestinal atrophy is discussed in Section E.

1. Influence of Absorptive Disorders upon Intestinal Digestion.

Although it is usual for a given lesion to affect both the motor and the secretory apparatus of the intestine at the same time, the following remarks are as far as possible restricted to cases of deficient assimilation of the chyme. This only makes itself manifest when the lesion extends over the greater part of the bowel, particularly the small intestine. Interference with absorption in the colon expresses itself mainly in increased amount of water in the fæces. The degree to which the healthy mucosa can compensate for that which is diseased has been ascertained from experiments upon animals [de Filippi (91)], and from observations upon the nutrition of patients in whom extensive portions of bowel have had to be resected. Schlatter (92), in a case of resection of 2 metres of small intestine, found the nitrogen lost in the fæces reached no higher than the maximum figures in healthy people, whilst the loss of fat was 14 per cent. Albu (93), under the same circumstances, found 10 per cent. nitrogen and 10·5 per cent. fat loss. Riva Rocci and Ruggi (94) investigated patients from whom about half the small intestine (3 to 3½ metres) had been removed. The nitrogen loss was 30 per cent. in the first case, 5 to 13 per cent. in the second; the fat loss, 23 per cent. in the first, 12 to 16 per cent. in the other. Albu and Ruschhaupt (95) conclude from these observations that up to one-third of the small intestine can be removed without harm, provided the diet be carefully attended to.

Localized passive hyperæmia, in cases of cirrhosis of the liver, appears to have no obvious effect upon food assimilation so long as it is not

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complicated by diarrhœa (96). There may perhaps be a slight diminution in the splitting up and resorption of fats [Bierens de Haan (97)]. In cases of general passive hyperæmia from heart failure, Grassmann (98) found more marked impairment of the digestion of fats, the loss in the fæces being upon the average 18 per cent. Proteins and carbohydrates, on the contrary, were assimilated normally. These conclusions are based upon six cases; but they are not generally applicable. Von Noorden's pupils, Vogel and Husche (99), several times found the resorption of fat to be undisturbed in spite of marked venous stagnation. It is only when there are widespread anatomical changes in the absorptive apparatus that food assimilation suffers severely—for example, in cases of tuberculous ulceration of the intestine, lardaceous disease or caseation of the mesenteric glands. The following figures exemplify this :

In lardaceous disease of the intestine, with tuberculosis of the mesenteric glands, the nitrogen loss was 12 per cent., the fat loss 33 per cent. [Müller].

In lardaceous disease of the intestine, with tuberculous peritonitis, the nitrogen loss was 14 to 27 per cent., the fat loss 31 to 37 per cent. [Weintraud (100)].

In tabes mesenterica the fat loss was 18 to 21 per cent. [Schmidt (101)].

Weintraud points out one characteristic of these disorders—namely, that the diminution in the absorption of fat always exceeds that of the protein. In disorders of the pancreatic secretion the assimilation of protein suffers more than does that of fat. Fr. Müller lays stress upon the fact that digestion of carbohydrate is not interfered with at all. Strasburger (84), however, has shown by careful investigation that it is slightly impaired. There can be no doubt that there are some purely functional disturbances in which the assimilation of meat alone is interfered with [Schmidt (90)]. It seems inadvisable, therefore, to make any hard-and-fast rule, or to say that in disorders of absorption the fats always appear in the stool first, the protein next, and the starches never at all.

In so far as defective assimilation leads to the presence in the lower parts of the bowel of a chyme rich in undigested food, it might well cause an increase in decomposition there. This is far from what actually occurs as a rule. Simple venous stagnation from heart failure leads to no increase in the aromatic compounds in the urine [Brieger, von Noorden (102)].

2. Influence of Absorptive Disorders upon General Nutrition.

The majority of disorders of resorption described above depend upon irreparable anatomical changes. When they result in manifest deterioration of digestion, the consequences soon show themselves in the general nutrition of the patient. Simple venous stagnation has but a slight effect upon digestive processes, and does not lead to inanition. The emaciation of patients with cirrhosis of the liver or chronic heart failure is due to other causes.

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D.—DISORDERS OF EXCRETION.

In addition to its other functions the intestine, as is well known, eliminates a variety of substances from the body fluids. It thus eliminates inorganic salts, such as those of iron, calcium and phosphoric acids. To a less extent it also excretes nitrogenous and fatty or fat-like bodies. Honigmann (103) showed that a larger quantity of iron and calcium than normal was retained in the body after extirpation of ½ metre of ileum.

Brauneck, von Noorden, and Ritter (104) observed an increased elimination of nitrogen in the fæces of those who have kidney disease. Weintraud (105) found an increase of alloxuric bodies in the fæces in a case of leuchæmia. In all these observations the intestinal excretion was concerned secondarily, by way of compensation for disease in other organs. It is possible that the same kind of thing may occur as a primary disorder. There are no positive proofs of this. It is interesting, however, to note that Soetbeer and Krieger (106) regard phosphaturia as caused by deficient excretion of calcium by the bowel. To enter more fully into their experiments at present would be premature.

E.—PROCESSES OF DECOMPOSITION.

Bouchard (107) and his pupils founded the doctrine of intestinal auto-intoxication. A somewhat airy superstructure has been rapidly built upon their teaching. It has led to general belief in the fact that decomposition in the alimentary tract plays a large part in the production of diseases and errors of metabolism. This is most clearly shown in Albu's (108) work, "Ueber die Auto-intoxikationen des Intestinaltraktus," which appeared in 1895. It required the sharply critical insight of F. Müller and Brieger (109) to sift the truth from amongst the theories that sprang up in all directions. Very little indeed is left after this sifting. One fact, however, becomes strikingly evident—namely, that the methods of estimating the amount of intestinal decomposition have hitherto been inadequate, since they do not lead to the detection of the suspected toxines. New methods are required. Without going into the entire question of intestinal auto-intoxications, a brief survey of the normal and pathological processes of intestinal fermentation and putrefaction may here be given.

It is well known that the intestine is the only internal organ in which from the day after birth onwards bacterial decomposition takes place continuously without the body suffering any necessary harm. The chemical processes that occur in decomposition of the chyme consist in fermentation of the carbohydrates, putrefaction of the protein, and conversion of the fats into the lower fatty acids. Of these, the last is of least importance. Fermentation of carbohydrates takes place normally, both in the lower part of the small intestine and in the colon. Putrefaction of protein, on the other hand, occurs exclusively in the large intestine.

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The ileo-cæcal valve forms a sharp line of demarcation, above which putrefaction of protein never occurs, except under pathological conditions. In the cæcum and ascending colon, which are the sites of most active decomposition, both fermentation and putrefaction take place together; the latter afterwards outruns the former, to decrease again in the last portion of the colon, where the fæces become inspissated. In correspondence with this it follows that the fæcal bacteria which flourish abundantly in the cæcum gradually diminish in numbers further down.

The products of fermentation consist of gases (CO_2,H_2,CH_4), volatile fatty acids (acetic, butyric, etc.), and lactic acid. They are for the most part absorbed by the intestinal wall. The gases are excreted again in the expired air. The fatty acids are either oxidized and expired, or eliminated unchanged in the urine. The fermentation products that are not absorbed are excreted either mixed with the fæces or as flatus.

Putrefaction of protein produces ammonia, sulphuretted hydrogen, and other gases (CO_2,H_2), and also a number of characteristic bodies, such as aromatic oxy-acids, phenol, indol, and skatol. These are also absorbed by the intestinal wall. The gases are expired. The other substances are either excreted in the urine as compounds of sulphuric or glycuronic acid, or to a variable extent remain in the fæces.

It follows at once from the variable behaviour of the products of decomposition that it is extremely difficult to estimate them in the excretions. It is correspondingly difficult to obtain any measure of the amount of decomposition taking place. Until recently, only the putrefactive products contained in the urine have been investigated, those of the fæces being neglected. It is impossible even to guess what proportion of all the decomposition products thus escape absorption; probably the amount is variable. The method of estimating the indican, which Jaffé introduced, is particularly open to objection. The amount of indican in the urine does not depend solely upon the amount of putrefaction in the bowel, or upon the degree of absorption by the mucosa. It also varies with the length of time the fæces remain in the colon, with the activity of peristalsis [Müller, Ortweiler (87)], and most of all with the site of putrefaction. If protein decomposition extends up into the small intestine, far greater quantities of indican appear in the urine than ever occur through resorption from the colon [Jaffé, Ellinger, and Prutz (87)]. The colorimetric test for indican, as it is generally used in clinical medicine, is undoubtedly useful; but deductions must only be drawn from it when due allowance has been made for the various factors mentioned above, and when clinical symptoms are made full use of at the same time. The method of estimating the ethyl-sulphuric acid in the urine proposed by Baumann (110) is not much better. Although by this test a large proportion of the decomposition products of protein, such as indol, skatol, phenol, and cresol, can be determined, yet it misses several others which are present in the urine at the same time, such as the oxy-acids and those portions of the substances enumerated above which have become combined with glycuronic acid. F. Müller (111) has further pointed out that the decomposition of protein under the influence of

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different bacteria does not always take place in the same way, nor give rise to always the same end-products. The most that can be said is that when the ethyl-sulphuric acids in the urine are *markedly* raised, increased intestinal putrefaction is probable. It is by no means justifiable to draw any conclusions from medium or small amounts; and unfortunately this fact has not been realized in the numerous researches that have been made by Baumann's method.

Experiments in which the products of fermentation and putrefaction found in the fæces have been used as a measure of intestinal decomposition have only quite recently been initiated. A. Schmidt (112) uses the incubator test, and therefore obtains only a broad survey of the matter. Baumstark (88) roughly estimated the indol in the fæces by Ehrlich's aldehyde reaction, and showed that when the indoxyl figures of both urine and fæces are added together, the measure of intestinal putrefaction is very different from that given by the indoxyl of the urine alone. Ury systematically determined the putrefactive and fermentative products in both the urine and the fæces, but his methods are too complicated for clinical use, and his results too few to permit of any deductions as to the output in pathological conditions (88).

If the question is to be solved by estimating the products of decomposition, the sum total of all the substances evacuated in the various secretions and excretions must be determined. This is hardly practicable in the case of products eliminated in the expired air, in flatus, and in sweat, and meanwhile one has to be content to select a few decomposition products which are not too volatile, and which are found almost entirely in the urine and fæces. Even then Müller's warning must not be forgotten, that the breaking up of food-stuffs by no means always follows the same course. In the case of carbohydrates, and to some extent of protein too, there is this further consideration—that the decomposition products, when formed and absorbed, are broken up to an unknown extent in their passage from the bowel to the urine. This is the case with the fatty acids. Under these circumstances Strasburger's (31) researches deserve special attention. He takes the amount of living and dead micro-organisms in the fæces to be a means of measuring decomposition. In this way much light has been thrown upon the question—for example, in cases of biliary obstruction, of diarrhœa, and of constipation. The results are, however, only a summary. They afford no details as to the type of decomposition, whether fermentation or putrefaction, and so on. They can only be made use of to a limited extent. Notwithstanding the work done by Adrian (113), Gans, and Roos (114) the relationship between the number and variety of micro-organisms flourishing in the bowel, on the one hand, and the excretion of enterogenous decomposition products in the urine on the other, is not yet clear.

Bouchard (107) and his pupils proposed another method for investigating intestinal putrefaction. They injected human urine, extracts of fæces, blood, sweat, etc., into the veins of rabbits, and determined the minimum lethal dose per kilogramme body-weight of animal. This amount, the "urotoxic coefficient," varies considerably in different diseases. It has been shown, however, by Müller and Brieger (109) that

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the whole method of experiment will not bear scientific criticism. It has never obtained a firm foothold in Germany, and it may be regarded as discredited.

The one thing patent is that but little is known concerning normal intestinal decomposition. Where can a line be drawn between normal and pathological decomposition? To what extent and under what conditions can normal products of putrefaction and fermentation cause the phenomena of disease? No definite answers can at present be given. If acetic acid, butyric acid, ammonia, sulphuretted hydrogen, indol, skatol, and so on, are regarded as harmful substances, their poisonous effects must not be overestimated. Herter (115), it is true, maintains that indol can cause headache and symptoms of neurasthenia, but Rovighi (118) only observed toxic effects in animals when he injected more than 1 gramme per kilogramme body-weight. Sulphuretted hydrogen is seldom present in the bowel in more than traces (116, 117), and much larger quantities can be injected into the rectum without ill-effects [Bergeon (118)]. Sulphuretted hydrogen does more harm if it occurs in the stomach or small intestine (see Stomach). As regards ammonia, it is readily converted into harmless urea. So far as we know, the volatile fatty acids, acetic and butyric, have no other action than one of local stimulation, even when they are present in quantity (119).

The number of putrefactive products which occur in the intestine only under pathological conditions, and to which any toxic action can be attributed, is remarkably small. Careful criticism is a necessity when perusing the numerous publications on the subject. No sooner had the occurrence of acetonuria in digestive disturbances been made known (120) than a host of observations followed. Von Jaksch, Lorenz, and more recently Deusch and Pettera (121), jumped to the conclusion that acetonuria and diaceturia in diseases of the alimentary tract were a direct proof of an intestinal auto-intoxication. β-oxybutyric acid has been observed in the urine under similar conditions, though less frequently, and they regarded this in the same light. To these bodies they attributed a number of nervous symptoms, such as fainting attacks, coma, convulsions, and so on. Meanwhile von Noorden and others (109, 122, 125) thought this to be improbable. Acetonuria and diaceturia occur in inanition without any digestive disturbance. They have been found under all sorts of conditions, whenever there is breaking down of tissue protein. They must be regarded as an accompaniment of abnormal acid formation in the organism, and as intermediary products of metabolism. Their appearance in the intestinal contents may well be due to their excretion from the blood. Their causal relationship with the nervous symptoms mentioned above is more than doubtful.

The question whether poisons from the intestinal canal may not cause an acid-intoxication is different. Keller (124) has suggested this as a cause of the extreme wasting of infants with diarrhœa and vomiting. He bases his belief upon the large quantity of ammonia in the urine in these cases. Czerny, Pfaundler (125), and other experts in diseases of children agree with him. One objection to the view is that the loss of weight in marasmic infants often begins before the onset of diarrhœa and

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vomiting [Heubner (126), Czerny]. This being so, it is possible that the hypothetical poison may have its origin somewhere else than in the intestinal tract.

The presence of ptomaines arising in the bowel contents has been pointed out by von Udransky and Baumann, Stadthagen and Brieger (127). It has been shown that, in cases of cystinuria, cadaverin and putrescin can be demonstrated both in the fæces and in the urine, probably reaching the latter after absorption. Roos (128) found them also in one case of malaria with blood- and mucous-diarrhœa, and in a case of cholera. There were no toxic symptoms in any of these patients. It could hardly be expected that the small amount of these two diamines present would have a poisonous action. Their presence is mainly of symptomatic significance, in so far as, outside the body, the diamines have hitherto been obtained only in association with other virulent poisons in putrefying mixtures such as old cholera cultures (Brieger). In a whole series of diseases the urine has been found to contain poisonous substances, ptomaines or toxines (129), but in all these cases there has been no evidence of their intestinal origin.

It has not yet been determined whether Brieger's toxalbumins, which have hitherto been obtained only from bacteriological cultures, play any part in the pathology of intestinal decomposition or not. Similarly the pathological significance of neurin and of mercaptan is theoretical only, although Brieger included them in his speculations upon the subject.

1. Relationship of Decomposition to Intestinal Digestion.

(*a*) *Disorders of Secretion and Decomposition.*

When speaking of secretory disorders, the effect which the absence of a single digestive juice has upon decomposition has been already discussed. The question may, however, be looked at from the reverse point of view: Does a primary increase in the processes of fermentation or putrefaction lead to disturbance of secretion? It seems very probable, but at present there exists no certain knowledge upon the matter.

(*b*) *Motor Disorders and Decomposition.*

Simple constipation leads to no increase of decomposition—at least, no such increase can be demonstrated. Nevertheless, all manner of symptoms have been attributed to unknown poisons which result from coprostasis. The commoner symptoms that have been ascribed to this cause are albuminuria, fever, headache, lassitude, fainting fits, and convulsions. It cannot be denied that, when the slowing of motility is not restricted to the colon, but spreads to the small intestine or affects the latter alone, these general symptoms often become much more intense. Even this is not a universal rule. They may attain such a degree of severity as to present the picture of collapse—for example, in cases of strangulation. An obstruction must be complete if it is to produce severe

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disturbance, on account of the fluidity of the chyme. The decomposition that occurs in the small intestine above such an obstruction leads to the formation of greatly increased quantities of normal decomposition products. The amount of the latter becomes far greater than it ever is in the colon (87), and this fact has led a number of writers (130) to believe in the "intoxication theory" of the phenomena of obstruction. Unfortunately the nature of the supposed poisons is at present unknown. Kukula (131), by extracting the bowel contents with alcohol in a case of strangulation, demonstrated a toxic substance whose reactions were those of an alkaloid. Albeck (132) found something similar. Nevertheless, the results must be interpreted with caution. The intoxication theory has a difficult position to maintain against the auto-infection and reflex theories of the phenomena of strangulation. The question will be found discussed by Müller (109) and by Nothnagel (74).

Diarrhœa is sometimes associated with an increase of decomposition, sometimes not. This is readily understood when it is remembered that there are various kinds of diarrhœa. Certainly it is rare to find diarrhœa due to a simple primary increase of peristalsis without the other functions of the bowel being simultaneously affected, and without inflammatory changes in the mucous membrane. The knowledge of such is limited to certain forms of "nervous" diarrhœa. In these cases, as one might expect, there is clinically no increase of decomposition (133). In other forms, particularly in artificial diarrhœa, decomposition is increased. To determine this, it is essential that the fæces should be examined as well as the urine (86-89). The reason for this lies in the readiness with which the serum and mucus secreted by the irritated or inflamed mucosa become decomposed; they afford a favourable medium for the growth of micro-organisms. If, in a case of diarrhœa of obscure origin, there are definite signs of increased fermentation and putrefaction, it may be concluded with great probability that the condition is not exclusively one of nervous diarrhœa (133).

Diminution and increase of intestinal decomposition are not necessarily the result of motor disturbances in the bowel; they may be the cause rather than the effect.

Normal products of decomposition, particularly the gases and the volatile fatty acids, stimulate peristalsis in the colon. If they are not formed in sufficient amount, constipation may result. Strasburger (89), upon the strength of his researches in weighing the bacteria of the fæces, has expressed the view that there is a decrease in intestinal decomposition in many cases of chronic habitual obstipation. Lohrisch (86) has recently brought forward evidence to show that, owing to the extraordinary resorptive power of the colon in these cases, deficient formation of products of fermentation and putrefaction is here really due to the small amount of food residue left for the bacteria to live upon. It is not improbable that this is really the cause of the constipation in many instances. The reverse relationship, diarrhœa from increased decomposition, is much more commonly met with. It is probable, as Müller (109) points out, that a considerable number of cases of infectious diarrhœa owe their origin to poisons taken in, ready formed, in the food. Such poisons occur in meat

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milk, and cheese. Other cases may be due to the excretion through the intestinal mucosa of poisons formed in diseased tissues elsewhere. Examples of this are the diarrhœa that is met with in septic conditions, in uræmia, in pneumonia, and so on. There are still left enough cases in which it is likely that the toxic substances are swallowed with the food. It is only necessary to refer to the different forms of infantile diarrhœa, the streptococcal diarrhœa of Escherich, that caused by the *Bacillus enteritidis* of Gaertner, and cholera. Although, strictly speaking, these are instances of infection intoxication, and not of intestinal auto-intoxication, it is not possible to draw any sharp distinction between the two. If only cases of simple increase of normal decomposition are to be admitted, the reader may consult the section on the Gastrogenous Disturbances of the Intestine, particularly as to the diarrhœa resulting from achylia.

(c) *Disorders of Absorption and Decomposition.*

An unusual amount of readily decomposable material in the lower parts of the intestine may lead to disturbances of absorption. This has already been mentioned in Section C. Of late years there has been a widespread belief that the occurrence of much fermentation and putrefaction lies at the root of the pathological condition which Nothnagel (134) drew attention to and called intestinal atrophy. Upon the same hypothesis an explanation of many other obscure general disorders has been built up. Infantile marasmus, pernicious anæmia, and certain forms of cachexia, illnesses which are commonly associated with diarrhœa and vomiting, have all been attributed to intestinal auto-intoxication resulting from atrophy of the mucous membrane of the bowel. As always happens when a new disease has not been sufficiently investigated, speculation about it runs rife. This is the case here. The more this theory has been tested anatomically and chemically, the more have its foundations tottered. To-day it must be admitted that there is probably no such thing as an intestinal atrophy in the anatomical sense. It is on this account that it was not discussed when speaking of resorptive disorders. It will be well to give a short summary of the present state of the question.

The investigations of Nothnagel were stated to have revealed the fact that the mucous membrane of the full-grown intestine, particularly of the cæcum, showed linear atrophy in 80 per cent. of all cases. Scheimpflug (135) found this atrophy in 96 per cent. of all intestines. In contradiction to this, Gerlach (136) maintained that the microscopical appearances, upon which Nothnagel and Scheimpflug had based their opinions, were artefacts, due to post-mortem putrefaction and meteorism. The appearances in question were desquamation of the epithelium, thinning of the wall, and flattening out of the tubular glands. Gerlach's contention was supported by other workers (137, 138). Indeed, Gerlach's view may be said to have been established—at any rate, in the great majority of cases. Nothnagel himself recognised this, and has changed his original view in the last edition of his "Erkrankungen des Darmes

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und Peritoneums " (74). He says that he may have been mistaken, and that the question whether or not an atrophy of the intestine ever occurs is now a perfectly open one. A few observers believe they have been able to verify Nothnagel's earlier results (139), and, notwithstanding Nothnagel's later views, they adhere firmly to their belief in intestinal atrophy as a pathological entity, and believe it to be the cause of marasmus in infants [Baginsky] and of pernicious anæmia. As regards the latter disease in particular, a view is now gaining ground that it may arise from intestinal auto-intoxication [Grawitz (140)] without any demonstrable anatomical changes in the bowel. It is held that gastrogenous disorders of the intestine, such as are frequently observed in achylia, may suffice to cause it. It seems more likely that when atrophic changes are found in the stomach and intestine in pernicious anæmia, both these and the anæmia itself are the result of toxic or infectious processes—that the atrophy is an associated and not a primary phenomenon [Faber and Bloch].

I have made systematic observations, counting the glands in intestines obtained from a number of cases of pernicious anæmia. The method suggested has been elaborated by Meyer (137). If I may give my opinion upon the question of bowel atrophy, I would say that I have repeatedly, but not invariably, found the greater part of the intestinal mucosa to be affected by chronic inflammatory changes. These are not sufficiently marked to merit the term " atrophy." There is no diminution in the total number of tubular glands worth mentioning. The resorptive area is not diminished. The conditions rather correspond throughout with the slight conditions of irritation, which are so often, though not constantly, observed during life in cases of diarrhœa. In pernicious anæmia I have never hitherto met with putrefaction or fermentation severe enough to justify the theory of intestinal auto-intoxication.

2. Relationship of Decomposition to other Organs.

(*a*) *Liver and Kidney.*

According to Boas (141), the amount and specific gravity of the urine are lowered when those processes occur which clinically give rise to an impression of intestinal auto-intoxication. Albumin and renal tube-casts are frequently found in cases of severe constipation [Kobler, Stiller (142)], in diarrhœa [Stiller], and in intestinal obstruction [Benini (143)]. The extent to which this is actually the result of increased decomposition in the bowel must at present remain obscure. It is noteworthy that Wallerstein (144) succeeded in producing albuminuria in experimental coprostasis. Albumoses have been occasionally found in the urine of patients with intestinal diseases by Maixner and Pacanowski (145). Chvostek and Stromayr (146) have recently drawn attention to the fact that albumosuria may occur from ulceration of the intestine. Possibly enterogenous albumosuria is only a resorptive phenomenon.[1] Bouchard and Hanot (147) regarded the increased size of the liver, which can frequently

[1] In regard to products of intestinal decomposition in the urine, *vide supra*.

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be demonstrated in conditions of chronic dyspepsia, as a consequence of intestinal intoxication. In this they rely upon experiments made upon animals by Boix (148), who claims to have produced cirrhosis of the liver by administering food containing acetic acid and butyric acid for long periods. Bouchard and Hanot also lay stress upon the occurrence of acute yellow atrophy as a result of sausage-poisoning. This teaching has hitherto found no adherents in Germany [Müller (109)].

(*b*) *Blood.*

Of all the blood diseases, chlorosis and certain forms of pernicious anæmia are most closely related to decomposition in the intestine. As is well known, chlorosis is frequently associated with a tendency to constipation, and this symptom—or, rather, the hypothetical decomposition processes which accompany it—is, according to many (147, 149), the fundamental cause of the disease. These writers, however, have hitherto brought forward no scientific proof of the supposed connection. Forchheimer, it is true, investigated the urine of chlorotic patients and found a substance which was insoluble in alcohol, toxic, and of the nature of a peptone. No great importance can yet be attached to the discovery, however, for the reasons previously mentioned.

The question of the enterogenous origin of pernicious anæmia has already been discussed. Attempts to attribute the disease to atrophic processes in the intestinal mucosa, or to toxic products from the bowel contents, have not hitherto been successful. Nevertheless, there are a number of investigators who adhere to the enterogenous theory of many severe and unexplained forms of anæmia. W. Hunter (151), to whom the theory was originally due, has recently laid particular stress upon inflammatory affections of the mouth and gums. His original view has recently been supported by E. Grawitz (140), who, with others, bases his arguments upon analogy with the anæmias caused by *Anchylostomum duodenale* and *Bothriocephalus latus*. There can hardly be any doubt that toxic products are secreted by these parasites.

The therapeutic effects that occasionally result from careful dietetic treatment are striking [Grawitz, Perutz, H. Schmidt (152)]. It is unfortunate that so few animal experiments have been made upon the question. Strauss (153), in contrast to Vanni, was unable to produce any blood changes by artificially closing up the anus in rabbits. The blood changes attributed to enterogenous anæmia are certainly not specific. Köttnitz and Vehsemeyer (154) suggest that leuchæmia can also arise from changes in the alimentary canal. It is worthy of remark that too little attention has been paid to the fact that the blood diseases may be primary, and the intestinal changes secondary to it.

(*c*) *Skin and Muscle.*

Many people, after partaking of certain foods and drinks, such as strawberries, crab, beer, etc., develop skin eruptions, such as urticaria and

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various forms of erythema. The food eaten may itself be good, and in no way tainted. This has given rise to the belief that these people have a special idiosyncrasy, and readily suffer from the phenomena of intestinal decomposition. It is thought that these particular foods produce gastric catarrh, which in its turn gives rise to increased putrefaction in the bowel, and that the urticaria is due to absorption of the products of this putrefaction. Albu (108) maintains this theory by adducing the fact that simple gastric catarrh, not caused by any particular food, may be followed by similar eruptions. He also points out that various substances, amongst them certain drugs, can lead to the appearance of the same kind of skin affections. Erythema and urticaria are particularly liable to follow digestive disturbances in children [*strophulus infantum* (155)]. Some other eruptions have been ascribed to intestinal decomposition—for example, acne, erythema nodosum [Moritz (156)], erythema scarlatiniforme [Deutsch (157)], pemphigus, and pruritus [Albu (108)]. Proofs of the supposed connection are, however, difficult to collate. It is true that Singer, Freund, and Mracek (158) showed that in marked cases there was an increase in the ethyl-sulphuric acid in the urine. However, aromatic products of putrefaction, which enter into combination with sulphuric acid, cannot entirely decide the question. The conclusion that an increased formation of ethyl-sulphuric acid indicates the presence of other poisonous putrefactive products in the bowel contents is too vague. In the meanwhile clinical coincidence of gastro-intestinal troubles and skin eruptions must be admitted.

The same holds good of *polymyositis acuta* also. Senator (159) and Albu (108) have each described a case which followed upon severe digestive disorders. In this connection there is the analogy with trichinosis to be considered.

(*d*) *Nervous System.*

Most of the symptoms which clearly result from the effects of intestinal decomposition are displayed by the nervous system. They are of the most varied kind. At one end of the series there is simple headache; at the other coma, convulsions and collapse. The more usual forms may be considered under the headings: (α) the general phenomena observed in cases of severe constipation; (β) tetany; (γ) epilepsy or eclampsia; and (δ) psychoses.

(α) *The General Phenomena observed in Cases of Severe Constipation.*—These include the nervous symptoms seen in chronic habitual obstipation: feelings of being out of sorts, lassitude, headache, giddiness, neuralgia, ill-humour, and so on. Leube and others regard these as due to mechanical reflexes. Müller and Nothnagel believe them to be signs of a neuropathic diathesis, aggravated by digestive disturbance. The adherents of the auto-intoxication doctrine [Bouchard, Senator, Albu] attribute them to increased intestinal decomposition. The latter explanation is at present by no means established, in that there is no proof that chronic obstipation causes any increased putrefaction in the bowel. Fainting attacks of gastro-intestinal origin, and the so-called dyspeptic

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asthma, have been discussed in the section upon Diseases of the Stomach. It has been claimed by Moritz and Ebstein (156-160) that pyrexia may also be produced by chronic coprostasis, but Küstner and Müller contradict this (162-169).

Clinically, the general nervous symptoms may be very obvious in cases of acute intestinal obstruction, with or without acute vomiting. These cases have been regarded by some observers as typical examples of intestinal auto-intoxications. Kohlhaas and others (163) have published cases of this sort. Coma, with or without delirium, convulsions and collapse, are the main features of the clinical picture which follows the subsequent emptying of the bowel. The fact that the fæces or the vomit has been very foul-smelling has been accepted as sufficient proof of the presence of intestinal toxines in many instances. Boas (164) has rightly pointed to the numerous cases of ileus with fæcal vomiting, in which all the signs of auto-intoxication are wanting. From the scientific point of view more exact proofs are required. It is precisely in these affections, rapid in their course, that it is extremely difficult to demonstrate toxic substances in the urine and fæces [Ewald]. Ewald (163), using Brieger's method, discovered a small amount of diamines in the urine in one instance. He found them to be non-toxic for animals. Albu (163) came to the conclusion that Griffith and Bouchard's methods were unreliable, and that even if the hypothesis of intestinal toxines is not actually given up, there are as yet no satisfactory methods of proving it.

(β) The relation of tetany to abnormal decomposition in the alimentary tract has already been discussed in the section upon the Stomach. Decomposition in the latter organ is far and away its most common cause.

(γ) Epilepsy and eclamptic conditions have sometimes been associated with marked acetonuria. On this ground von Jaksch and Lorenz (121), in particular, have suggested intestinal auto-intoxication as their cause. Deutsch and Pettera (121) favour this view. Baginsky (165) denies any causal connection between convulsions and acetonuria—at least, in childhood. Acetone excretion may perhaps depend on accompanying intestinal disorders, as Baginsky allows. There are, however, many cases of acetonuria in which there are no convulsions, and still more instances of convulsions without acetonuria. This is the final conclusion drawn by Müller (109) from experiments upon strychnine tetanus and genuine epilepsy. Müller, in common with most pathologists, looks for the source of acetone, not in the bowel, but in an intermediary stage of metabolism.

(δ) Of late years, in France, there has been considerable discussion upon the connection between intestinal decomposition and psychoses. Out of these has crystallized the doctrine of "visceral psychoses." Mairet and Bosc (166), and also Brugia (167), found the toxicity of the urine to be increased in various forms of insanity (Bouchard's method). Voisin and Pervu (168) noted the same in cases of epilepsy. Griffiths isolated an alkaloidal substance from the urine of epileptics. These results appeared to afford a secure basis, upon which Régis (169) and others proceeded to build an airy castle of hypotheses. In Germany these

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theories have hitherto found but few supporters [Jauregg (170)]. It is needless to criticise them after the discussion at the beginning of this chapter.

3. Relationship between Decomposition, General Nutrition, and Protein Metabolism.

The question arises whether increased decomposition in the bowel leads to excessive destruction of protein, and thus causes serious ill-effects. The matter is of particular interest in connection with progressive pernicious anæmia and with infantile marasmus. The relation between these two affections and increased intestinal putrefaction has not yet got beyond the stage of hypothesis, as we have seen already. As regards pernicious anæmia, Rosenquist (171) has recently proved beyond doubt that a pathological increase of protein katabolism occurs periodically, both in that form produced by *Bothriocephalus latus*, and in those varieties whose origin is obscure. On the other hand—at least, in the cryptogenetic forms—there are other occasions when protein anabolism takes place. In the cases met with in achylia gastrica Strauss and Backmann (172) found the protein metabolism to be normal.

It is well known that loss of protein and fat occurs in the fæces in marasmus [Baginsky (173)]. The question arises whether or not an actual breaking down of tissue protein takes place independently of the impaired resorption. Keller (124) found remarkably large quantities of ammonia in the urine of these patients, and believed, therefore, that tissue protein was being destroyed.

Lange and Berend (174), on the other hand, dispute this. The whole question, so far as the action of intestinal toxines is concerned, is not yet ripe for full discussion.

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CHAPTER V

DISEASES OF THE LIVER

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Introduction.

In consequence of the many functions of the liver, the changes which may occur in disease are varied and numerous. These changes are brought about in the following ways :

1. In conditions of disease the secretory function of the liver may be so affected that either the formation of bile suffers or the outflow of bile is restricted. It is still a moot question whether certain liver diseases are associated with a primary disturbance of bile formation. On the other hand, pathological conditions are extremely common in which the outflow of bile is rendered difficult and stagnation follows as a result. The metabolic disturbances dependent on these conditions have been studied in the various clinical forms of jaundice.

In cases of uncomplicated stagnation of bile the metabolic disturbances develop in two directions :

(*a*) The lack of bile in the intestine influences digestion and absorption, altering the processes of absorption of fat and putrefaction, etc. (see Chapter IV.).

(*b*) As a consequence of the stagnation, biliary constituents pass through the lymph vessels of the liver into the blood and into the tissues.

2. The internal secretion of the liver cells is concerned in the second series of metabolic disorders in diseases of the liver [Minkowski, R. Kolisch (1)].

Besides the elaboration of the bile, the liver performs for the organism still other important functions, which play their part without causing an external secretion to be poured out. In this group belong, among others, the formation of glycogen from sugar and the reconversion of glycogen into sugar ; the synthetic processes, such as that of the amido-acids and ammonia into urea ; the neutralization of extrinsic or intrinsic toxines ; the conjugation of aromatic bodies with sulphuric and glycuronic acids. All of these functions are localized in the narrow space of the liver cell, and are, therefore, of the true internal-secretory type.

A priori, it is not to be expected, therefore, that a single definite result follows the action of a definite poison upon the liver cell. Hence there

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are no functional disturbances of the liver cells, which are pathognomonic for absolutely definite changes of the hepatic parenchyma. The metabolic disturbances following injury of the liver cells by simple stagnation of bile, by infectious or toxic jaundice, by cirrhosis of the liver, by acute yellow atrophy and phosphorus-poisoning, show no characteristic difference, but rather only quantitative variations. As every disturbance of the activity of the cells ordinarily influences the proper performance of other functions, a number of phenomena are combined in the symptom-complex of hepatic insufficiency.

In what follows an attempt is made to give a survey of the collective disturbances of metabolism observed in diseases of the liver, and, indeed, to value these disturbances, not so much from the general pathological point of view as, rather, from their practical clinical significance. The subjects are arranged, therefore, from their clinical rather than from their pathological standpoint.

From what has been said it is self-evident that such a grouping must lead to repetitions. In order to limit this, the individual questions of general hepatic pathology are always more or less exhaustively treated when they are met with for the first time, thus anticipating their later appearance.

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I.—INFLUENCE OF STAGNATION OF BILE UPON THE METABOLISM.

Metabolic Disorders Associated with Jaundice.

In this connection jaundice is interpreted as being synonymous with stagnation of bile, and with a complete or partial exclusion of bile from the intestine. More weight is, therefore, laid upon the clinical phenomena of icterus than upon its pathologico-anatomical cause and upon the degree of stagnation.

The reasons for a separate consideration of this symptom are evident from the following:

1. Stagnation and exclusion of bile from the intestine produce, depending on the cause, a number of peculiar resulting phenomena, which always repeat themselves, partly as the only expression of the entire disease—as, for instance, in occlusion of the ductus choledochus—partly as accompanying phenomena of other metabolic disturbances.

2. All the known forms of jaundice are, as regards their final etiology, brought about singly and alone by stagnation of bile. They are also all of hepatogenous origin in the old sense of the word.

The disturbance in the outflow of bile leads to an absorption of bile within the liver, and induces a jaundice, owing to the passage of biliary constituents into the blood and tissues.

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(*a*) The pathogenesis of this condition is clear and self-evident in all those cases in which the stream of bile is blocked in the large intrahepatic bile-ducts, or even in the ductus choledochus, by catarrhal inflammation of the mucous membrane, gall-stones, tumours, etc. Owing to the low secretion pressure of the bile, a relatively weak obstruction is sufficient to prevent, more or less completely, the bile from reaching the intestine. The stagnated bile is absorbed within the liver into the lymph channels which surround the smallest bile-ducts, and thus, without the liver cell itself being necessarily primarily affected in the slightest degree, the pure obstructive (resorptive) jaundice may arise.

The metabolic disturbances in obstructive jaundice may limit themselves to the lack of action of bile in the intestine and to the appearance of biliary constituents in the blood, tissues, and finally in the urine. If, however, under the influence of biliary stagnation, the liver cells later suffer injury, then secondary disturbances of their internal-secretory activity arise.

(*b*) Less clear is the occurrence of biliary stagnation in cases of jaundice in which the larger bile-ducts are entirely free from any apparent obstruction, and in which a palpable reason for the stagnation of bile and its absorption in the liver is not directly recognisable.

Pathology has formerly classified these cases as anhepatogenous (hæmatogenous) jaundice. The biliary pigment content of the blood, tissues, and urine should, then, be traceable to the solution of the blood pigment (hæmolysis) and the intravascular conversion of hæmoglobin into bilirubin (2).

From the experimental investigations of Naunyn and his students the proof has been forthcoming that the conversion of hæmoglobin into bilirubin takes place only in the liver in those pathologic conditions in which a considerable dissolution of red blood-corpuscles in circulating blood doubtless occurs under the influence of protoplasmic poisons. Hence to-day no further doubt exists that also in those cases in which bilirubin passes into the tissues and colours them yellow the biliary pigment is a product of the liver cell.

The cause of the absorption of bile in the liver is in these cases the quality of the bile, which is secreted more abundantly, thus causing jaundice by polycholia, or which has become richer in pigment, thus bringing on jaundice by pleiochromia. Both factors are influenced by the great abundance of decomposing red blood-corpuscles, which serve as material for the formation of biliary pigment.

Indeed, it must be granted that in devitalized blood, as in thrombi and extravasations, small amounts of biliary pigment may be formed from the derivatives of the blood pigment (hæmatoidin = bilirubin). True jaundice never results from such formation of biliary pigment, as the amount of the pigment so formed is not sufficient, and its absorption is too slow, to bring about such a condition. We recognise an anhepatogenous formation of biliary pigment from the blood pigment, but only an hepatogenous jaundice [E. Stadelmann (3)].

Increased decomposition of blood furnishes the material for the more marked formation of biliary pigment in the production of a true tissue

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jaundice. Considered from the experimental evidence, the cycle of events in cases of dissolution of blood (hæmocytolysis) is as follows :

If dissolved hæmoglobin circulates in the blood, the kidneys and the liver are concerned in its excretion, the former, however, only under the assumption of a very marked hæmoglobinæmia. Three phases of this condition present themselves :

(*a*) In marked hæmoglobinæmia, the conditions of hæmoglobinuria, excretion of hæmoglobin in the bile (4, 5), and increased formation of biliary pigment occur (6).

(*b*) In cases showing a medium degree of hæmoglobinæmia the bile contains hæmoglobin and there is an increased excretion of biliary pigment.

(*c*) In slight hæmoglobinæmia only the biliary pigment is increased.

In other words, after it has held the hæmoglobin in combination as insoluble parhæmoglobin [Kobert], the liver, with perhaps the assistance of the spleen and leucocytes [Tirmann, Joannovics (7)], elaborates into biliary pigment small amounts of dissolved hæmoglobin. With larger amounts this normal function of the liver is insufficient, a part of the hæmoglobin passes unchanged into the bile, and as a consequence of the overloading of the blood with free blood pigment the kidneys are called upon to aid in the excretion of this hæmoglobin. As soon as the formation of biliary pigment in the liver is greatly increased, as a result of the large supply of dissolved hæmoglobin, the bile assumes a tenacious consistency, which renders the outflow difficult owing to the slight secretion pressure in the liver. Hence stagnation and absorption must occur behind the sluggishly advancing stream of bile.

The " pleiochromia of the bile " [Stadelmann (8)], which is brought about by the influences causing dissolution of the blood-corpuscles, is, however, not the only factor contributing to this tenacious property of the bile, and to its stagnation and absorption. Under the influence of the same injurious action there arises simultaneously a catarrhal inflammation of the smaller bile-ducts, which contributes to the biliary stasis by increased mucus formation [Stadelmann, Hunter (9)]. Inasmuch as Cornil and Hanot had formerly explained the occurrence of jaundice following cirrhosis of the liver and infectious processes by obstruction of the smaller bile-ducts, infective cholangitis, along with toxic cholangitis, has in recent times been granted a large share in the pathogenesis of absorptive jaundice, largely independent of the pleiochromia of bile [Naunyn]. In human pathology also cholangitis has, as a matter of fact, assumed greater importance in the pathogenesis of jaundice than has pleiochromia of bile, which is brought about by the dissolution of the blood-corpuscles. Although, as in animal experiments, true stagnation of bile may be brought about in man through the influence of hæmolyzing agents (such as ether, chloroform, snake venom, arseniuretted hydrogen, phosphorus, toluylendiamine, mushrooms, aniline, laktophenin, bile salts, chlorates, hæmolysins, tuberculin, transfusion of blood of different species, lightning flashes, etc.), yet there are, nevertheless, cases of hæmoglobinæmia and hæmoglobinuria in which, notwithstanding the opportunity afforded of increased formation of biliary pigment, every

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disturbance in the outflow of bile is lacking. Likewise, there are experimental cases in which no jaundice is observed in dogs, in spite of hæmoglobinocholia and hæmoglobinuria following large injections of hæmoglobin [Schurig, von Stark (5)].

The increased formation of biliary pigment, if considered alone, is not a sufficient and decisive cause, and it could not be so in all cases of jaundice following infectious diseases, such as septico-pyæmia, yellow fever, pneumonia, and typhus, in which there can be anatomically demonstrated, on the other hand, the inflammatory changes in the smaller bile-ducts and the mechanical obstruction to the outflow of bile [obstruction of the biliary capillaries either by swelling of the liver cells, the so-called "Dislocation des travées" of Hanot], or by biliary thrombi, Eppinger (11).

On the basis of the experimental investigations of Stadelmann, Naunyn, Minkowski, Silbermann, Quincke, Afanassiew, which are comprehensively elaborated in Stadelmann's monograph (3), it is essential that there be accepted for all these forms of jaundice a formation of biliary pigment in the liver, deviating from the normal at most only in a quantitative aspect, and also an intrahepatic absorption of bile; while, on the other hand, a hæmatogenous origin of jaundice must be rejected.

While in the pathogenesis of the above-mentioned forms of jaundice the discussion has had reference only to disturbances in the outflow of bile, for other cases in which no sufficient evidence of a mechanical hindrance to the outflow of bile is given a functional disturbance of the liver cell has been assumed in explanation of the passage of bile into the blood.

The disturbance might consist in this: that the diseased liver cell, as a result of a sort of anomalous secretion, diverts the biliary constituents which it has elaborated towards the side of the cell where lie the blood-vessels ["Parapedesis of Bile," Minkowski (12)]; or that the cell has become absolutely unable to retain the biliary pigment, so that this diffuses into the blood [diffusion jaundice, acathectic jaundice, Liebermeister (12)]; or at least an abnormal direction of the current arises [paracholia, E. Pick (12)].

The assumption of an alteration in the liver cell is a plausible explanation of all cases in which untoward influences of infectious or toxic origin have affected the organism. It is almost self-evident that the active toxins in these cases injure, either directly or indirectly, the liver parenchyma to a more or less extent, just as they harm the red blood-corpuscles, which they cause to disintegrate. Moreover, chemical and morphological changes of the bile—such as content of albumin, appearance of liver cells, and of cylindrical epithelial casts [Brauer (13)]—point to the fact that the elements (liver cells and the small epithelial lined interlobular bile-ducts) which are concerned in the formation of bile have to do with such cases.

It is, however, difficult to decide whether a direct passage of biliary pigment from the liver cell into the blood, as Minkowski assumes, is connected with the alteration of the liver cell, or whether there occurs also a purely mechanical stagnation of the bile, even in the intercellular bile capillaries, until they finally rupture and discharge their contents

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into the perivascular lymph spaces, as Eppinger advocates. Thanks to the newer histological technique of staining, which has made it possible to demonstrate not only the intra-acinous bile capillaries, but also their entrance into the liver cells, a repetition of the classic experiments will give much wider information concerning the pathogenesis of jaundice.

With such a diverse origin of the cases, which show at the sick-bed the symptom-complex of jaundice, it is not to be expected that all cases of icterus are, as a group, characterized by the same disturbances of metabolism. Just as in the course of jaundice different etiologic factors are concerned in a variable manner in the pathogenesis of icterus, so with the same patients at different times constantly changing reactions of the jaundice upon the metabolism may occur. This is shown, for instance, when an originally mechanical biliary stasis leads in its turn to a severe injury to the liver cells, which endangers the elaboration of their internal secretion; or when, on the other hand, a mechanical obstruction to the outflow of bile follows as a result of tenacity of the bile or of anatomical changes in the liver (such as swelling of the liver cells, proliferation of connective tissue, etc.), depending on the way in which the liver cell alone was originally affected by the untoward influence.

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A.—INFLUENCE OF STAGNATION OF BILE UPON THE GENERAL METABOLISM AND NUTRITION.

Regarding the caloric consumption and the oxygen need of the icteric patient, no investigations are accessible. Yet there is no evidence which could possibly point to the assumption of higher or lower values than the normal.

In individual cases of simple chronic biliary stasis a reaction upon the general condition of nutrition is completely lacking even after long-continued and complete occlusion of the bile-duct. More often, however, the state of nutrition suffers, as is shown by a loss of weight, which points to a retrogression of the bodily activities.

The cause of this condition of lowered nutrition lies in part in the poor fat absorption of the icteric, hence such patients should be allowed little fat in their diet. By exclusion of fat from their diet the calorie value necessary for the maintenance of metabolic equilibrium is meanwhile very difficult to reach, and can be attained only by providing a large amount of food.

The icteric suffers chiefly from partial loss of appetite, or else from digestive disorders which follow each hearty meal, and make it necessary for the physician to discontinue a too liberal diet, so that a condition of undernourishment results in many cases. Although, as has been shown by Voit and Winteler (1) in their experiments on dogs with biliary fistulæ, the possibility theoretically exists of sufficiently nourishing the patient by increasing the protein and carbohydrates of his diet, in spite of exclusion of bile from the intestine, yet this point is often not attainable, and the patient is forced to utilize his own body fat, or fat and protein, to make up his needed calorie value.

B.—INFLUENCE OF JAUNDICE ON THE PROTEIN METABOLISM.

The icteric patient is, as a result of undernutrition, often compelled to use up his own tissue protein. Whether, in addition to the above factors, the stagnation of bile comprises other influences prejudicial to the life of the cell—in other words, whether toxogenic decomposition of protein takes place—is another matter. Theoretically, this assumption depends upon the fact that certain constituents of the bile are protoplasmic poisons [Rywosch, Naunyn (2)]—as, for instance, the bile acids, which hæmolyze the red blood-corpuscles, although they are only present in traces in the blood of the icteric patient.

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Unfortunately, only a very few exact quantitative investigations of the metabolism of the icteric are known. The urea excretion has been worked out by the French school, but in the experiments recorded the diet was not sufficiently controlled. The following details reported by Fr. Müller deserve, however, careful consideration (3)[1] :

		Calories in Daily Food.	*Nitrogen per Day.*		*Nitrogen Balance.*
			Absorbed.	In Urine.	
1	Emaciated man, icterus with gall-stones	1,082	Gm. 10·19	Gm. 10·85	Gm. −0·66
2	Man, 57 kilogrammes, gall-stones: liver cirrhosis ..	1,610	14·11	15·88	−1·77
3	Man, 57 kilogrammes, gall-stones: liver cirrhosis ..	883	17·18	17·14	±0

In these experiments, in which the food was, although rich in protein, nevertheless low in calorie value, and therefore deficient, little or no nitrogen was lost from the body. Hence the protein decomposition did not exceed normal limits.

The researches of Riecke (3) teach the same thing. Two patients with catarrhal jaundice, and one healthy control person, placed on the same simple diet, showed an average daily nitrogen excretion, the former of 10·5 and 9·9 grammes, and the latter of 9·7 grammes. In these cases the differences in protein decomposition were therefore minimal. Schupfer confirmed these results.

In the case of a markedly jaundiced elderly woman with carcinoma of the gall-bladder, who died three months later from cachexia, I found the following values :

Food Calories.	*Nitrogen.*	*Urine Nitrogen.*	*Fæces Nitrogen.*	*Nitrogen Balance.*
	Gm.	Gm.	Gm.	Gm.
2,340	11·14	11·53	0·86	
2,340	11·14	10·05	0·86	−0·94
2,340	11·14	10·20	0·86	
2,400	12·54	11·01	0·79	
2,400	12·54	8·64	0·79	+4·8
2,340	11·14	9·88	0·69	
2,340	11·14	9·16	0·69	+1·7

In contrast to the above cases, the enormous loss of nitrogen (up to 12 grammes per diem) during the height of the disease which R. Schmidt (4) reported in a patient with catarrhal jaundice can scarcely be explained without the assumption of a toxogenic decomposition of protein. To be sure, owing to the anorexia of the patient, a marked degree of undernourishment (3·8 grammes of protein with a total calorie value of

[1] The tables of F. Müller, which are intended to represent only the absorption relations, are changed in this place and the calculation of the calories is given ; in doing so, however, only the calories of the actually absorbed food, the so-called pure calories, are considered.

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600) had taken place on the corresponding days, which condition caused in its turn a further decomposition of protein. However, the losses of nitrogen are greater than one would expect in absolute inanition, and hence we must assume, on the basis of these careful metabolic investigations, that stagnation of bile may accompany protein decomposition in the course of simple catarrhal jaundice characterized by a correspondingly long course and by intensity of the icterus.

With some reservation, the sulphuric acid determinations of Biernatzki (5) might be considered in deciding the question at issue. Biernatzki found, in two cases of catarrhal jaundice in which the food remained the same day by day, the daily sulphuric acid excretion to be :

Case.	*In Jaundice Period.*	*Post-Jaundice Period.*
1	0·8920 gramme.	1·0419 grammes
2	1·9399 grammes.	2·1762 ,,

It is to be born in mind that in early jaundice relatively more sulphur is separated in the neutral form, and therefore the sulphuric acid estimations are at fault. Thus, if the total sulphuric acid excretion, and consequently the protein decomposition, be estimated both in the period of jaundice and in that of convalescence, the results will approximately agree in both cases. The question has been repeatedly and thoroughly studied in animals. In experiments of thirty-three to fifty days' duration Wilischanin ligatured the ductus choledochus in dogs, and determined that in the first period after this procedure the protein decomposition was pathologically increased. Kratkow (5) investigated in sixteen of such dogs the exchange of gases and the excretion of urea, uric acid, and of sulphuric and phosphoric acids, up to the time of their death, which occurred when a loss of 30 to 40 per cent. in weight was observed.

C.—INFLUENCE OF JAUNDICE ON THE INTESTINAL PROCESSES.

The bile first becomes mixed with the ingesta in the upper part of the duodenum, so that disturbances in the digestive tract, as a result of exclusion of bile, do not occur above this point.

Of the changes in the secretion and composition of the saliva in cases of jaundice nothing is known. In two cachectic patients, with occlusion of the ductus choledochus due to carcinoma, I failed to obtain the sulphocyanate reaction in the saliva. This reaction is not invariably present in health.

A constant influence of biliary stasis on the secretion of gastric juice has been many times affirmed, but the data at hand are very contradictory. Von Jaksch (6) found a diminished hydrochloric acid secretion in certain cases of catarrhal jaundice, while von Noorden (6) showed a normal hydrochloric acid content following a test breakfast in each of three cases of cholelithiasis and two cases of catarrhal jaundice. Riegel (6) reports similar results, and I have records of acidity of 38 to 68 decinormal nitric acid in five of my cases of catarrhal jaundice and of jaundice

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following cholelithiasis. Leva (6), on the contrary, failed to detect the free hydrochloric acid in four such cases during the icteric period, and saw it reappear only after the icterus had subsided.

According to Hayem (6), hyperchlorhydria usually occurs in jaundice. Simnitzky (6) investigated the chemical composition of the gastric contents in twelve icteric patients (seven cases of catarrhal jaundice, one of Weil's disease with hepatic colic, three of hypertrophic cirrhosis, and one of jaundice as a result of compression of the ductus choledochus by a carcinoma of the pancreas). In all eighty-one analyses were made of the contents withdrawn after a test breakfast, the free hydrochloric acid, the combined hydrochloric acid, and the total chlorine content being determined. In the majority of cases a hyperacidity was found, in which the free acid was the chief factor; hence a hyperchlorhydria must be admitted in cases of biliary stasis. This concession permits the conclusion that an increase of the secretory activity of the stomach occurs as a result of the stagnation of bile. As the retention of bile is less marked, the composition of the gastric contents returns again to the normal values, and conversely rises again to hyperacidity following renewed biliary stagnation. Thus the increased secretory activity of the stomach arises from the retention of bile. Hyperacidity fails only in those cases of catarrhal jaundice in which there exists at the same time an inflammatory condition of the stomach.

Regarding the influence of biliary stagnation on the absorption of food in the intestine, as well as on the putrefactive processes in the alimentary canal, see the chapter on Diseases of the Intestine.

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D.—REACTION OF STAGNATION OF BILE ON THE FUNCTIONS OF THE LIVER.

After long-continued biliary stasis both the external and the internal secretory functions of the liver are disturbed. Such disturbances necessitate the conception of biliary stasis within narrower boundaries. Attention may be first directed in this connection to the conditions in which the jaundice is due to an obstructed outflow of bile into the intestine. In those cases in which the jaundice is brought about through stasis of bile in the biliary capillaries, or by parapedesis, the liver cell in the beginning plays such an important rôle in the pathogenesis of the jaundice that it is impossible to distinguish how far the metabolic disturbances are dependent on the injury to the liver cell, or, secondarily, on the biliary stagnation.

1. Disturbances of Bile Production.

The disturbances of bile formation, as a result of biliary stasis in the above sense, must be first considered. These conditions cannot be directly analyzed, because we cannot control during life the amount and composition of the secreted bile. There are, however, sufficient data at hand which point to the manifestation of such disturbances in a twofold manner, with frequent transition of one condition into the other:

1. By overloading of the blood with biliary constituents and by lack of bile in the intestinal contents.
2. By the direct injurious influence of the stagnated bile upon the liver cell.

(*a*) *The Amount of Bile.*

So long as the obstruction of the bile-duct continues, the amount of bile is lessened in every case of biliary stasis in the narrow sense. There must be an enormous absorption of fluid directly from the bile-ducts if the bile, under conditions of obstructed outflow, is to be secreted in the ordinary amount (400 to 500 c.c. per diem at least).

After the obstruction is removed, the secretion soon becomes abundant. Since operative procedures are often adopted in cases of old-standing biliary obstruction, the opportunity of examining the bile which flows freely from the operative fistula sometimes arises.

Thus Yeo and Herroun (1) found, in a case of carcinoma of the ductus choledochus, an average daily excretion of 374 c.c. of bile, containing 1·35 per cent. of total solids. Copeman and Winston (1) obtained an average amount of 779 c.c. of bile from a fistula of the gall-bladder arising from perforation during an attack of cholelithiasis. A patient of Bain's (1) excreted, as a daily average of sixteen days, 775 grammes of bile, with 15·8 grammes of dry residue, while Albu's patient excreted 400 c.c. of bile on an average. Brand has collected, along with the reports of nine of his own analyses, the remaining extensive data regarding human bile (1).

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(*b*) *Biliary Pigment.*

In obstructive jaundice biliary pigment is freely formed. As this pigment is a conversion product of hæmoglobin, hæmoglobinæmia, hæmoglobinocholia, and hæmoglobinuria ought to occur if the elaboration of hæmoglobin into bilirubin were restricted in the liver. In simple obstructive jaundice, even in the severest cases, there is no such course of events. Only when the destruction of the red blood-corpuscles (hæmolysis) assumes unusual proportions under the influence of the poisons circulating in the blood does the conversion of hæmatin into bilirubin fail to keep pace with the supply of blood pigment.

Theoretically, it is conceivable that the bile pigments may be increased in jaundice. The circulating biliary pigment—which escapes excretion in the urine or deposition in the tissues—is returned to the liver, and again placed at the disposal of the liver cell for excretion. Where biliary pigment is injected intravenously into animals, it is promptly appropriated by the liver cells, no trace of it appearing in the urine nor pigmentary increase occurring in the bile [Tarschanoff, Vossius (2)].

On the other hand, it has not been proven that the liver normally obtains from the intestinal canal the material from which it elaborates the biliary pigment, nor that such pigment is absorbed and again used by the liver in the formation of bile [Naunyn (2)]. The production of biliary pigment in the liver need not also suffer on account of the lack of bile in the intestinal contents. As a matter of fact, the considerable quantity of bile pigment which is daily eliminated in the urine of old-standing cases of biliary obstruction clearly proves that the stasis of bile does not injure the pigment-forming functions of the liver cell.

Yet a suppression of the production of bile as a result of biliary stasis has been many times assumed. From his observations on decolorized excreta of patients showing no trace of jaundice, Ritter (3) first arrived at his idea of colourless bile (*la bile incolore*). This led him later to explain the autopsy findings of an apparent œdema of the gall-bladder ("colourless ropy contents of the gall-bladder") by the production of colourless bile, and to see in these findings a sign of a pathologic function of the liver. The presence of bile acids and of cholesterin in the pigment-free fluid seemed to justify this view, which is accepted by Harley and Hanot in their analogous clinical observations.

In the further elaboration of the theory Hanot and Robin (3) added to this *acholie pigmentaire*—in which only the formation of biliary pigment is at fault—the *acholie des acides biliares*, and the *acholie totale*. Without being related to a definite form of liver disease, acholia is especially noted in diffuse tuberculous disease of the liver [Letienne (3), Hanot], in fatty liver, and in many forms of cirrhosis.

This theory of acholia advocated by the French authors has never been accepted in Germany, the recorded observations being far from convincing. When colourless fæces are passed by non-icteric patients, the quantity of fat and the presence of leuko-urobilin are in all cases accountable for the clay-like colour of the stools. Should an obstructive

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jaundice return in the course of the disease, while the stools remain apparently colourless [Hanot, Budd (3)], there is no reason for assuming that colourless bile now enters the intestine, as the pale colour of the stools may be explained in the way already mentioned. Finally, the passage of the bile acids into the urine in such cases [Robin], and their presence in the colourless contents of the gall-bladder, must be proven in a more conclusive way before this theory can be accepted.

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Urobilinuria.

Relative to the formation of biliary pigment in the diseased liver, much discussion has been focussed upon the question of the presence and meaning of urobilin (hydrobilirubin). The following are the facts:

In slight degrees of jaundice of diverse origin, in which the fæces still contain derivatives of biliary pigment, either urobilin and bilirubin, or urobilin alone, are present in normal or increased amount in the urine. In light catarrhal jaundice, in incomplete occlusion of the bile-duct by calculi, in the light yellow cutaneous pigmentation which occurs in many acute infectious diseases, and, further, in acute and chronic poisonings, such as alcoholism and saturnism, in patients with uncompensated heart lesions, and in those with cirrhosis of the liver, these relations are modified, but maintained (1).

In jaundice of a severe type, with total occlusion of the ductus choledochus, the urine contains bilirubin, but no urobilin (2). The fæces in these cases likewise contain little or no urobilin [F. Müller], nor do they contain any of its leuko-product, urobilinogen [Neubauer (3)]. If bile be given *per os* in such cases, urobilin reappears in the urine soon after the entrance of biliary pigment into the intestinal canal [Fr. Müller].

When the occluded duct is reopened, the bilirubin in the urine quickly diminishes, and the urobilin content of the urine, therefore, reaches very high values (1 and 2). Thus, for example, the urine of a patient of Müller, with lead colic and light jaundice, contained 10·988 milligrammes of urobilin (about the normal amount); the jaundice disappeared after a

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few days. There was found in the urine 29·106 milligrammes (three times the normal amount), and in the fæces 1942 milligrammes urobilin (twenty times the normal value).

There is, as a rule, no parallelism between the excretion of urobilin in the fæces and in the urine [D. Gerhardt (4)]. That such is the case is shown in the table below, in which are collected the few existing comparative estimations of urobilin in the urine and fæces.

As the individual workers have employed different methods in their quantitative determinations, the figures are not exactly comparable with one another. They agree, however, in this point: that in cases of liver disease, especially liver cirrhosis, the urobilin content of the urine is relatively great as compared with that of the fæces.

Subject.	*Author.*	*Urobilin.*	
		Urine.	Fæces.
		Mgm.	Mgm.
Convalescent	Gerhardt (4)	24·0	1170·0
,, ...	,,	42·0	1617·0
Tuberculosis	Ladage (5)	73·7	120·4
Convalescent	,,	56·4	130·3
Pleurisy	,,	67·0	128·8
Multiple sclerosis	,,	95·5	130·6
Cardiac disease	Müller (2)	21·6	104·9
Cirrhosis of liver	,,	93·4	187·6
,, ...	Ladage (5)	178·3	158·8
,, ...	,,	169·2	188·7
,, ...	,,	169·7	177·4
,, ...	,,	175·6	156·8
Lardaceous disease	,,	200·6	143·2
Carcinoma of liver	Gerhardt (4)	208·0	623·0

Along with the occurrence of urobilin in the urine and fæces, its presence in the bile has also been observed. Confirming this latter statement, there are the opportune observations of Jaworski, Pentzoldt, Mya, and Meinel (6), in which a rose coloration of the vomited bile-containing stomach contents is noted on allowing the vomitus to stand exposed to the air.

Systematic experiments have shown that the bile often contains urobilinogen (3, 7, 8). Urobilinogen is lacking in the bile only after complete closure of the ductus choledochus or hepaticus [Neubauer (3)], or after profuse diarrhœa [Kimura (8)]. Urobilin is, likewise, not contained in the bile in these cases [F. Müller (7)].

From these facts and their associations several theories of urobilinuria have been built up. They differ essentially from one another in that the formation of urobilin is localized at different places in the body, and also in that the source of urobilin differs according as bilirubin or hæmoglobin is assumed to be the mother-substance of this pigment.

In discussing these theories, it is not allowable to proceed from the assumption that the urobilin in the urine in cases of urobilinuria of

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healthy and diseased men is the same pigment, and identical with the stercobilin found in the normal stools ; and, further, it may not be maintained that the hydrobilirubin which may arise from pure bilirubin by reduction is identical with urobilin and stercobilin. MacMunn (9) has shown that a difference exists between the normal and the febrile urinary urobilin. The identity of the urinary and fæcal urobilin (which shows the same chemical composition) with the hydrobilirubin obtained from bilirubin has been doubted by Le Nobel (9), and lately, on the basis of their analyses, by Hopkins and Garrod (9). On the other hand, that the fæces and the urine contain the same chromogen, and that from this the corresponding pigment (hydrobilirubin or urobilin) is formed under the influence of sunlight, and that by strong reduction the same pigment may be obtained from bilirubin, which itself is changed into urobilin by the action of light [von Leersum (9)], are arguments which, viewed from the standpoint of their agreement as regards chemical reactions and spectroscopic relations, have been advanced in favour of the identity of these pigments.

It is not possible to bring into accord with these views the fact that the normal urinary urobilin, in distinction from the pathological and from the fæcal hydrobilirubin formed from biliary pigment by reduction, is an oxidation product of bilirubin [Le Nobel, Stokvis, Heynsius and Campbell, Jolles]. Urobilin, according to these investigators, is identical with choletelin.

1. *Theory of Hepatogenous Urobilinuria.*

The normal liver cell produces bilirubin, while the pathologically active liver cell forms urobilin, the amount formed being an indication of the degree of hepatic insufficiency [Gübler, Dreyfuss-Brissac (10), MacMunn (9), Tissier (10)]. This theory of urobilin formation, which is to-day still accepted in France, arises from the assumption of *ictère hémaphéique* by Gübler—a form of jaundice in which biliary pigment is associated with other pigments, chiefly urobilin, in the urine. The hæmaphein must arise in the liver directly from the blood pigment, when this is carried to the normal liver in excessive amount as the result of a marked disintegration of red corpuscles (relative insufficiency of the liver), or when the liver cells themselves suffer from disease (absolute insufficiency of the liver).

2. *Theory of Hæmatogenous Urobilinuria.*

The liver cell has nothing to do with the formation of urobilin. This formation is much more directly dependent on the decomposition of the red corpuscles. In the test-tube, blood-serum containing hæmoglobin after a time shows the presence of urobilin without putrefactive processes taking place [Winter]; the change occurs by erythrocytolysis, and is similar to that which occurs in hæmorrhagic infarcts, extravasations by retrogressive metamorphosis, or by infectious material and

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chemical poisons in the blood-current itself [Poncet, Viglezio (11)]. The frequent presence of urobilin in old hæmorrhages (11) may be cited in confirmation of such a direct urobilin formation from hæmoglobin. However, such a formation occurs only when there is no other source from which the urobilin might be introduced into the exudate. Of the greatest importance in this regard is Gerhardt's discovery of urobilin in the blood-stained ascitic fluid of a case of carcinoma of the gall-bladder, in which, as a result of occlusion of the cystic bile-duct, the intestine was free from biliary pigment and urobilin.

In itself, the direct derivation of urobilin from hæmoglobin is more easily understood to-day, since it has been shown that the energetic reduction of hæmatin leads, not only to hæmatoporphyrin, but to urobilin, via mesoporphyrin and hæmopyrrol, which is known to be a urobilinogen [Neubauer (3), Nencki and Zaleski (12)].

Also the simultaneous occurrence of urobilin and hæmatoporphyrin in cases of lead-colic, pneumonia, liver cirrhosis, and sulphonal-poisoning, or of urobilin alone in a case of trional-poisoning [Beyer (13)], makes it probable that urobilin as well as hæmatoporphyrin can be formed directly from the blood pigment independently of the activity of the liver. However, the bile also contains hæmatoporphyrin in these cases, so that the pigment formation both of urobilin and of hæmatoporphyrin may have taken place in the liver through intervention of the liver cells.

3. *Theory of Nephrogenous Urobilinuria.*

Urobilin is formed neither in the diseased liver cell nor in the circulating blood. The liver cell always produces only bilirubin. If, however, bile is absorbed, as in cases of jaundice from stasis, then the biliary pigment is carried through the blood-current to the kidneys, where the epithelium of the kidneys reduces it to urobilin, which then appears in the urine.

Von Leube (14) accepts this view because he found bilirubin, but no urobilin, in the sweat of a patient with urobilinuria. The detection of bilirubin in the blood in almost all cases in which the urine contains only urobilin led von Jaksch (14) to adopt this theory, which Patella and Accorimboni also accept. The supposed frequent absence of urobilinæmia with strong urobilinuria speaks likewise for this theory [Herscher (14)].

4. *Theory of Histogenetic (Pigmentary) Urobilinuria.*

The liver itself produces only bilirubin. After this has, in cases of jaundice, been taken up into the blood-current, and partially deposited in the tissues, it is there converted into urobilin to a certain degree as a protective measure against the toxic action of bilirubin. Depending on the extent to which this happens, the very diffusible urobilin passes out of the tissues and appears in the urine, in contradistinction to bilirubin, which is firmly combined in the cells [Kiener and Engel, Kunkel, Cordua, Pellaconi, Mya (15), Patella and Accorimboni].

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The fact that bilirubin, and even its higher oxidation products, biliverdin and choletelin, are transformed into urobilin under reducing influences is the basis for this theory.

5. *Facts of Enterogenous Urobilinuria.*

None of the above theories are tenable [see the criticism to which they have been subjected by D. Gerhardt (1), F. Müller (2), and von Noorden (16)]. At the most it can only be assumed that a formation of urobilin from blood pigment direct [Nencki (12), Gerhardt (4)], or under the influence of autolytic processes in the liver [Magnus-Levy (17)], may occur. The occurrence of a urobilinuria in this way is not as yet proven, and even the presence of urobilin in the hæmorrhagic ascites due to occlusion of the bile-duct is not entirely conclusive, inasmuch as, in such cases of chronic stasis of bile, small amounts of biliary pigment constantly pass into the intestine through the intestinal wall, and are there formed into urobilin.

According to F. Müller (2), the enterogenous origin of the pigment upon which the formation of urobilin depends is the only point proven. The pathogenesis of urobilinuria may be presented as follows :

The liver cell, both in normal and abnormal conditions, forms only bilirubin from the blood pigment. Providing there is no marked obstruction to the passage of bile into the intestine, the bilirubin is acted upon by bacteria, which reduce it so completely to urobilin [Salkowski-Leube, Jaffé (18), Fr. Müller (2)] that only traces of bilirubin appear in the fæces [Fr. Müller (2), J. Rosenthal (18)]. A part of the urobilin is absorbed, and is excreted in the urine, while traces appear in the bile [Jaffé, Fr. Müller, Kimura (8)] and in pathologic transudates and exudates [D. Gerhardt (4), Ajello (11)]. When bacterial action is excluded, as in the new-born, no urobilin is found in the urine [D. Gerhardt]. Further, when bile is not present in the intestine, as in cases of absolute occlusion of the ductus choledochus, urobilinuria does not occur. It is sparingly excreted when the production of biliary pigment is diminished, as in hunger, while the amount is small, or at most normal, in cases of incomplete exclusion of bile from the intestine. On the other hand, the amount excreted may reach abnormal limits if a preceding obstruction, accompanied by stasis, has been overcome, and bile flows freely into the intestine. Likewise, the quantity may be abnormally large if the production of biliary pigment from the red blood-corpuscles increases as a result of infection and intoxication, or of hepatic lesions, such as cirrhosis and cyanotic induration. In these cases the bile is tenacious, and the condition may give rise to jaundice, although it is seldom that the stasis is so great that the bile is completely shut off from the intestine. Indeed, in most cases, owing to the excretion of excessive pigment in the bile (pleiochromia), a more than normal amount of pigment passes into the intestine [Stadelmann (19)], and as a result of this there arises a marked urobilinuria, with a mild degree of biliary stasis. In many cases the stagnation of bile is great enough to cause a passage of biliary pigment from the blood into the urine, leading to a marked urobilinuria, a mild

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degree of bilirubinuria, and a yellow tinting of the tissues. In other cases the absorption of bile is so slight that only yellowing of the tissues results, yet the concentration of pigment in the blood does not suffice to permit of its excretion by the kidneys, so that marked urobilinuria, and yellowing of the tissues without bilirubinuria, ensues. This symptom-complex is frequently noticed in acute infectious diseases, especially pneumonia and malaria; also in valvular heart lesions, in absorption of hæmoglobin from hæmorrhagic infarcts and apoplectic foci, lead-poisoning, cirrhosis of the liver, carcinoma, etc. To this complex the name *ictère hémaphéique* [Gübler (19)], or urobilin icterus [C. Gerhardt (20)], was formerly applied, but the term is no longer tenable, since Quincke (2) and von Leube (14) have shown the presence of bilirubin in the pigmented cutaneous areas of these patients, and especially since the whole series of symptoms may be traceable to simple, but incomplete, stagnation of a bile overloaded with bilirubin. This explanation, in which the pleiochromia of bile is really made accountable for the pathologic urobilinuria, is, however, not entirely satisfactory, inasmuch as it does not explain many of the clinical symptoms.

Moreover, the amount of fæcal urobilin in normal fæces is not inconsiderable, although the normal urine only occasionally contains traces of urobilin. The urine, however, does contain the chromogen [Saillet (21), Neubauer (3)], yet the amount of urobilin to be derived from this is extremely small in comparison with that found in pathologic urobilinuria. If, with such a normally marked urobilin content of the intestinal canal, urobilinuria is not a regular physiological phenomenon, then the only explanation available is that, along with the extent of urobilin formation in the intestine, a second factor presents itself as intimately connected with the excretion of urobilin in the urine. The same conclusion follows a consideration of the fact that pleiochromia of bile, upon which basis pathological urobilinuria is obliged to rest, is hypothetical for at least a part of the cases. It is true that in liver diseases, especially in cirrhosis, pleiochromia is most frequently present, yet here also it is not a constant condition [A. Schmidt (22)]. If, however, in such cases the reduction of the bilirubin (which is passed into the intestine in excessive amounts) be limited by administration of calomel, even then the urobilin excretion in the urine is not always correspondingly diminished, least of all, apparently, in cases of undoubted atrophic cirrhosis of the liver. In such cases I was usually able to extract urobilin from the green stools following the administration of calomel. Likewise, in a case of cyanotic induration of the liver, with noticeably green stools, I observed a large excretion of urobilin, which I was able to " salt out " of the urine with ammonium sulphate [Weintraud]. However, before definite conclusions may be made, further exact quantitative researches along these lines are required.

Finally, it has been experimentally shown that pleiochromia of bile, or, rather, passage of increased amounts of biliary pigment into the intestine, does not at all increase the excretion of urobilin in the urine, but does rather increase the urobilin content of the fæces [Ladage (5)]. Thus, after administration of 100 milligrammes of bilirubin *per os* during five

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to seven days, the excretion of urobilin increased on an average as follows :

Case.	*Urine.*	*Fæces.*
	Mgm.	Mgm.
1	73·76–83	120–158
2	56·47–67	130–187
3	67·02–74	128–196
4	95·54–98	130–199

For the occurrence of urobilinuria the amount of pigment is not so important as is the degree of absorption of the pigment from the intestinal canal; hence it is necessary to know upon what this absorption depends, and to find out as far as possible just what portion of the intestine is concerned in the absorption.

As a rule, the formation of urobilin in health takes place exclusively in the upper part of the large intestine [Macfadyen, Nencki and Sieber, A. Schmidt, Schorlemmer (23)]. Here the conditions do not appear to be especially favourable for its absorption, and, indeed, they are so much the worse the more the fæces are dehydrated.

Urobilin, which appears higher up in the bowel, seems to be completely absorbed. In the four cases already mentioned, Ladage found an increase of the urobilin excretion following the administration of 100 milligrammes of urobilin *per os.*

Case.	*Urobilin.*	
	Urine.	*Fæces.*
	Mgm.	Mgm.
1	73–128	120–130
2	56–126	130–130·7
3	67–133	128–127
4	95–185	130-145

Similarly, the observation of a marked urobilinuria after the introduction of urobilin-containing bile into the stomach [Meinel (6)] points to an extensive absorption of urobilin from the upper segments of the small intestine.

In cases of pathological urobilinuria either the biliary pigment which pours into the intestine with the bile is, indeed, reduced to urobilin in large amounts in the small intestine, or preformed urobilin passes into the upper intestinal segments, in these cases in larger than normal amounts. Its only possible source is the bile, which regularly contains urobilinogen, and usually urobilin. Indeed, it is only in cases of complete occlusion of the bile-duct that the bile is free from urobilin [Fr. Müller] and from urobilinogen [Neubauer, Kimura]. Thus, urobilin disappeared from the bile of a dog with a biliary fistula just as soon as the ductus choledochus was ligatured, and reappeared at once on the administration of bilirubin with the food [A. Beck (7)].

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Consequently, there exists normally a circulation of urobilin from the intestine into the blood, through the liver and bile, back to the intestine [Vitali, Fr. Müller (24)]. The question is, therefore, to be considered whether a disturbance of this circulation, in the sense of an overloading of the intestines with urobilin, may play a part in the causation of pathologic urobilinuria. An absolute increase in the supply of biliary pigment to the intestine (pleiochromia), and an increased formation of urobilin therefrom, would not, then, be absolutely essential. It may be that the liver normally regulates this circulation as follows: The urobilin, arising in the intestine, and absorbed from thence, is carried to the liver by the branches of the portal vein, where it is held back more or less completely in order to permit of its reconversion into biliary pigment [Vitali (7)]. In this respect the liver is at fault, when as a result of functional insufficiency, with an excessive supply of pigment, or as a result of anatomic changes, even when the demand for such activity does not exceed the normal, the urobilin is not properly retained and reconverted into bilirubin. The urobilin is then taken up by the blood and lymph streams either directly in the liver or in the small intestine, into which the urobilin is introduced with the bile, and from which it is completely absorbed [Ladage]. In spite of the usual presence of urobilin and urobilinogen in the bile, these are not ordinarily found in the small intestine [Macfadyen, Nencki and Sieber, A. Schmidt (23)].

In accepting an exclusively enterogenous origin of urobilin, we arrive at a hepato-intestinal pathogenesis of urobilinuria, in which the liver is assigned a part which it can adequately assume in all pathological conditions characterized by urobilinuria.

In his hepato-intestinal theory of urobilinuria, Riva ascribes to the liver a somewhat different action in the causation of this condition. In pathologic conditions, especially in diseases of the liver, a bile is formed in which the power of reduction of bilirubin to urobilin is greater than normal, as a result of the presence of certain substances (presumably ferments) which arise in the liver (25).

Riva acknowledges the reconversion of urobilin into biliary pigment in the liver, and also adds confirmatory evidence to this idea by his animal experiments, in which injection of urobilin into the blood was followed not by urobilinuria, but by bilirubinuria. Likewise, urobilinuria does not follow injections of urobilin into the peritoneal cavity of dogs unless the liver cells have become insufficient as regards their power of utilizing urobilin, as a result of a preceding excessive drain upon the hepatic activity by injection of bilirubin or of hæmoglobin [Vitali]. Just so the liver of phosphorus-poisoning is, in contradistinction to the healthy liver, not in a condition to bring about a conversion of hæmatoporphyrin into bilirubin [Auguste Pi Suner (25)].

Hence the hepato-intestinal theory of urobilinuria, outlined above, corresponds most closely to the clinical observations and experimental findings of the urobilin problem. Many points in the theory require further confirmation. To this end there are needed qualitative and quantitative researches, which comprise not only fæces, urine, and bile, but also blood and pathologic exudates, and which must always consider

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not only the urobilin, but also at the same time its leuko-compound, urobilinogen. Ururosein [Rosin (26)], which is always present in traces in normal urine, and in more perceptible amounts in pathologic urine, must not be ignored, for this is easily formed by oxidation of urobilin on treatment with calomel [Zawadski (26)]; and if Riva and A. Garrod (27) are right in their assertion that the yellow pigment of normal urine is also an oxidation product of urobilin (obtainable by treatment with potassium permanganate), then the amount of this urinary pigment, which is so difficult to estimate, must be taken into consideration. Such inquiries may later lead to unanimity regarding this difficult chapter of the theory of metabolism, which has already been so greatly advanced by numerous ingenious investigations.

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(c) *Bile Acids.*

In the discussion of the protein decomposition of the icteric patient a contradiction must be apparent. The bile acids are protoplasmic poisons, and yet this property of those which are absorbed into the blood does not regularly express itself in the metabolism of the icteric individual. This fact leads to the investigation of an old and much-discussed question —namely, the fate of the bile acids in jaundice. In reality their amount in the urine is not great in cases of biliary stagnation. Thus, E. Bischoff (1) found 0·34 gramme per diem, and this value has been exceeded

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in later analyses only by a few centigrammes. As a rule, only traces are present. Malkoff, for instance, in one-fourth of all his cases of jaundice, failed absolutely to find the cholate. On the other hand, Ajello and Lacace found traces present in all their cases of icterus. The normal amount of bile acids produced in man is 8 to 10 grammes per diem. If this production continues in jaundice in the same proportions, then either large amounts must accumulate in the blood and tissues, or must be utilized in the metabolism. The first hypothesis surely cannot hold, otherwise marked and quickly produced phenomena of poisoning would be absent when there was no biliary stasis.

Therefore the assumption was made very soon after the discovery of the bile acids that in jaundice a part of the acids are destroyed in the blood, and thus become harmless [E. Bischoff, Hoppe-Seyler, Bunge (1)]. This was supported by the observation of Bischoff that only a small part of the daily production of bile could be obtained from the fæces (4 grammes out of a daily formation of 8 to 10 grammes). And so to-day this hypothesis, which von Leyden (1) energetically opposed, is generally accepted, and needs no further elaboration. Stadelmann (2), in supplementing the earlier researches of Huppert, Röhrig, Schiff, and others, conclusively proved that in dogs almost all the bile acids which were injected into the blood-current were not oxidized, but were again excreted with the bile. Further, in collaborative investigations with Nissen, Loewenton, Winteler, and Gertner (3), Stadelmann determined that two-thirds of the amount—oftentimes more—of the bile acids administered *per os* reappear in the bile within ten to twelve hours. Tappeiner, who detected bile acids in the lymph of the thoracic duct, and Croftan, who showed their presence in circulating blood, therefore confirm the previous observations.

If these results are applied to human pathology, it is easy to understand why, on exclusion of the bile from the intestine, the excretion of bile acids with the bile is at once so markedly diminished. The circulation of the bile acids is interrupted, and correspondingly only in the first days after the appearance of the obstruction of the bile-duct are the bile acids found in icteric urine in appreciable amounts. After a few days the bile acids diminish, and only traces are demonstrable [W. Legg, Cahen, Fr. Müller (4)].

Comparable to these results is the record that the neutral sulphur is increased in the urine—presumably as a derivative of taurocholic acid [Lépine]—only in the days immediately following the biliary obstruction; yet this finding has been recently disputed by H. Benedict and R. Schmidt (5), the latter referring, on the contrary, the very high values which he found for the excretion of the neutral sulphur at the height of a catarrhal jaundice to the absorption of considerable amounts of bile acids.

At all events, besides the interruption of the circulation, a further explanation is still necessary for the diminished production of bile acids in jaundice. For those cases of jaundice in which the fæces continually contain bile the foregoing ideas do not suffice, because there is no interference with the circulation of bile acids at such times. Also it has been

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experimentally shown that in many cases of poisoning—as, for instance, in poisoning with sulphuretted hydrogen [Stadelmann (5)], which causes jaundice by pleiochromia of bile—the production of bile acids is markedly diminished, while the formation of biliary pigment is at the same time excessively active. Hence the liver cell, which has been damaged by the poisonous action, is no longer able to produce the bile acids, although the material for this synthesis is not lacking.

It is possible that the conditions are the same in man if the liver cell is functionally disturbed by the stagnated bile. Numerous analyses have been made of human bile from fistulæ of the gall-bladder following a preceding long-continued biliary stagnation. Many of them are characterized by a very slight yield of bile acids—as, for example, the bile analyzed by Yeo and Herroun, which contained only 0·055 per cent. of sodium taurocholate, and 0·165 per cent. of sodium glycocholate, the normal content in bile acids being over 2 per cent.

From what has been said it is self-evident that one may properly expect to obtain normal bile from a biliary fistula only when the daily amount of bile given is administered *per os*, or when only a relatively small part of the produced bile escapes through the fistula and the chief part is poured into the intestine.

Very few, indeed, of the biliary secretions which have been hitherto analyzed have been obtained under these conditions. Brand (6) has collected the analyses of such biles. These showed absolutely normal values for the bile acids in two cases, one of cholelithiasis and one of hydatid cyst of the liver. No mention was made in these cases of the length of time the stasis had existed prior to the operation.

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2. Storing of Glycogen in the Liver—Alimentary Glycosuria and Lævulosuria.

It is necessary to form a guarded opinion concerning the experiments on the glycogen content of the liver, yet a few observations appear to admit of no other interpretation than that obstruction to the outflow of bile hinders the storing of glycogen in the liver.

J. Wickham Legg (1) found, after ligature of the biliary duct, that Claude Bernard's *piqûre* was without effect. From this result, as also from the findings of von Wittich, Külz and Frerichs, and Cohnheim (1), it has been inferred that glycogen disappears from the liver after ligature of the biliary duct. This same result is given by the researches of Dastre and Arthus (1), which strikingly illustrate the relation of biliary stasis to disappearance of glycogen. These investigators ligatured the individual branches of the hepatic duct, so that the liver became only partially icteric ; the icteric areas of the gland then contained less glycogen than the healthy portion. Likewise Hergenhahn (1) found only traces of glycogen in the liver of rabbits after tying the bile-duct, although he attempted to promote a storing of glycogen by special feeding, as well as by injections of cane-sugar.

It does not follow from these experiments that the liver does not still form glycogen, but only that it has lost its power of storing glycogen. If this reasoning is correct, and is applicable to man, then it is probable that, under conditions which require the collaboration of the liver for the preliminary storing of large amounts of carbohydrates, the icteric patient would show more easily than the healthy an alimentary glycosuria after a rich glucose intake.

Külz and Frerichs failed, without exception, to find sugar in the urine of such individuals on ordinary diet, and this agrees with the results of routine clinical examinations upon jaundiced persons [von Noorden (2)]. It is, therefore, astonishing that certain observers consider glycosuria to be a usual accompaniment to cases of cholelithiasis. Gans (2) recorded that glycosuria was a constant symptom in a series of cases, both during and immediately after the attack, and Finkler (2) confirms this. Exner's similar results in 40 cases have been so adequately criticised by Naunyn, Kausch, and Zinn (2), that the glycosuria present in doubtful cases of cholelithiasis may be considered as of little diagnostic import.

In order to prove whether alimentary glycosuria appeared more easily in icteric individuals than in the healthy, Frerichs (3) administered 100 to 200 grammes of glucose in nineteen cases of hepatic disease. The only two cases in which traces of glucose were found in the urine were not of obstructive jaundice, but of phosphorus-poisoning ; in the seventeen remaining cases he failed to find the slightest trace. Roger (3) recorded positive results in two cases of catarrhal jaundice and in one of cholelithiasis ; while of the four cases of obstructive jaundice reported by Bierens de Haan, two showed a mild grade of alimentary glycosuria after 150 grammes of cane-sugar. On the other hand, von Noorden (2) never observed glycosuria following the administration of 150 grammes of glucose to the fasting patient, and also Strauss (3) regularly failed to

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find an excretion of sugar in four cases of catarrhal jaundice and three of cholelithiasis, two of which were icteric.

If one considers that healthy persons also excrete small amounts of sugar during the first hours after taking 100 to 200 grammes of glucose, especially if the glucose is not absolutely pure, then it follows from the experiments reported hitherto that stagnation of bile does not facilitate alimentary glycosuria in man.

It is not possible, for the present, to bring these facts of clinical observation into proper agreement with the experience of animal experimentation, and with the views regarding the rôle of the liver as a storehouse for glycogen, yet the liver of icteric patients appears to be just as intolerant to accumulation of glycogen as does that of rabbits and dogs. By exploratory puncture of the liver in a case of severe icterus with suspected abscess of the liver, cells were obtained which showed microscopically no trace of glycogen [von Noorden (3)].

Likewise, there is no evidence for the view that the excess of carbohydrate in cases of biliary obstruction is deposited in the muscles so much more abundantly than is normally the case. In the above-mentioned investigations, E. Hergenhahn (1) found low glycogen content not only in the liver, but also in the muscles of rabbits, after ligature of the bile-duct.

In clearing up these relationships, still other factors must be considered, of which we know absolutely nothing at present. Von Reuss (3) could not determine that lowering of the glycogen content of the liver regularly occurred in rabbits after ligature of the ductus choledochus.

The occurrence of alimentary lævulosuria, which Strauss (3) first observed in diseases of the liver, throws a certain light on the phenomena. Although the condition is not limited to cases of biliary stagnation, but occurs generally in hepatic lesions, it should still be discussed in this connection. H. Sachs (4) noted a lessened tolerance for lævulose in frogs after removal of the liver, while the assimilability of glucose, galactose, and arabinose was unaltered. Strauss showed that alimentary lævulosuria occurs in the majority of cases of liver diseases when 100 grammes of lævulose is taken by the patient during fasting. These results have been widely confirmed (4). Slight variations are found only as regards the frequency of the lævulosuria. After considering all the available experiments (seventy-seven), Strauss concludes that about 80 per cent. of all patients with liver disease react toward addition of lævulose by an excretion of sugar, while only 4·5 per cent. of all hepatic cases show an alimentary dextrosuria.

The fact that patients with liver diseases have a lower limit of assimilation of lævulose than the healthy individual cannot, therefore, be doubted. This is the more remarkable, as normally the tolerance for lævulose is by no means less than for glucose [Fr. Voit, von Noorden (5)]. Likewise in rabbits the limit of toleration is approximately the same for both kinds of sugar [F. Blumenthal (5)]. In dogs, lævulose is but rarely less well tolerated than is glucose [Schlesinger (5)]. The diagnostic meaning of alimentary lævulosuria is thus open to criticism.

As Minkowski's investigations have already shown that the normal

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liver under certain conditions (as after extirpation of the pancreas) behaves quite differently toward lævulose than toward glucose, forming glycogen from the former, but not from the latter, so the alimentary lævulosuria of the hepatic patient teaches us, further, that the liver occupies in the body a more isolated position towards the utilization of the lævorotatory sugar than it evidently does in relation to the assimilation of glucose.

In cases of diminished functional activity of the liver, the system cannot call forth certain vicarious functions which protect it from an overloading of the body fluids with lævulose, for, as Strauss has shown, this sugar appears in the blood after administration of 100 grammes (6). It is possible that the muscles play a subordinate rôle in the formation of glycogen from lævulose, or that the utilization of lævulose is closely related to the normal function of the liver. This is, indeed, contradicted by the fact that even after the liver has been removed, small amounts of lævulose are tolerated without excretion of sugar.

The observation of Sehrt (6) that a pancreas muscle mixture is not able to decompose lævulose while it uses up glucose likewise points to the fact that, in the consumption of lævulose in the system, the muscles do not render assistance to the same extent as in the utilization of glucose.

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3. Urea Formation.

In the liver certain stages in the intermediary metabolism of protein are completed. Ammonia is transformed into urea [von Schröder], although the liver is by no means regarded as the only place of urea formation in the organism of mammalians [Nencki and Pawlow (1)]. Doubtless, also, there exist relations of the functions of the liver to the formation of amido-bodies (such as leucin and tyrosin) from protein, and to cleavage of the ammonia (necessary for the formation of urea) from the amido-acids [M. Jacoby (1)]. Less certain are the relations of the liver to the purin bodies (uric acid, xanthin bases) and to the albumoses and peptones.

There remain to be investigated whether, in individual diseases of the liver, the urine yields any information regarding marked disturbances of these relations; likewise whether, instead of the end-product of protein decomposition—namely, of urea—intermediary products appear which, like ammonia and the amido-acids, may be regarded as precursors of urea; and, finally, whether a lessened activity of the liver may be made entirely responsible for this insufficient conversion of nitrogenous substances.

In simple biliary stasis, at all events, the liver completely satisfies the demands of the protein decomposition. Isolated observations of leucin and tyrosin in the urine of icterics [Ruge, Chittenden, L. Langstein] do not prove the contrary any more than does the presence of albumoses, which Pacanowski found, while O. Brieger failed to discover them in his cases (2).

All these bodies are formed during autolysis of the liver [M. Jacoby (1)]. If leucin and tyrosin appear in the urine, they can be regularly found in the degenerated liver. While their occurrence in the urine in small amounts betrays a degenerative process in the liver, yet it does not show an inhibition of the oxidation of the normal decomposition products. Small circumscribed areas of necrosis of the liver cells are—judging from animal experiments—somewhat frequent in cases of simple biliary stasis (2).

The formation of urea is rarely affected. Mörner and Sjöquist found,

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in a case of long-continued obstructive jaundice, 85·6 per cent. of the urinary nitrogen in the form of urea, 8·1 per cent. as ammonia, and 6·3 per cent. divided between uric acid and other nitrogenous bodies (3). Von Noorden, in collaborative investigations with Friedrichsen, showed in five cases of simple biliary stagnation (two cases of catarrhal jaundice and three of cholelithiasis) 80 to 87 per cent. of the nitrogen as urea and 4·9 to 9·5 per cent. as ammonia, the sum of the urea and ammonia nitrogen reaching 87 to 94 per cent.

In the recent series of investigations, in which the urea was estimated by the only method free from objection—namely, Schöndorf's (3)—only two cases of jaundice are found. In one of these, a case of jaundice as a result of carcinoma of the ductus choledochus, reported by von Jaksch (3), 85·6 per cent. occurred as urea nitrogen, 2·8 per cent. as amido-acid nitrogen, and 6·7 per cent. as nitrogenous bodies precipitable by phosphotungstic acid. Since, according to Landau's (3) estimation (by Schöndorf's method), the urea nitrogen of the healthy subject amounts to 90 per cent. of the total nitrogen on an average, von Jaksch's figures point to only an insignificant lowering of the urea formation. Unfortunately, the ammonia nitrogen has not been separately estimated in this case, so that we are in doubt whether the lessening of the urea occurred at the expense of the ammonia. The relatively slight increase of amido-acids comes, therefore, so much the less into consideration, as this is, at the same time, a question of the increase of hippuric acid.

Halpern (3) reported the partition of the nitrogenous substances in the urine of another icteric patient as follows :

Urea nitrogen	=	86·55 per cent.
Purin bodies nitrogen	=	2·64 ,,
Ammonia nitrogen	=	3·63 ,,
Amido-acids nitrogen	=	2·39 ,,
Extractive nitrogen	=	4·79 ,,

Thus there was no marked lowering of the urea, and that, too, was not to the advantage of the ammonia.

An analysis of the urine of a case may be reported here in which, although the stools were free from bile, yet the urine contained no biliary pigment, so that we must assume a deficient secretion of bile rather than an obstruction of the biliary duct. Moraczewski (3) found in this case 7 to 15 per cent. of the total nitrogen in the form of ammonia nitrogen—quite a substantial increase of ammonia. Since no urea estimations were made, and the determined uric acid values were very low, it remains doubtful whether one is justified in considering this to be a case of restriction of the urea formation from ammonia.

Simnitzki and Rodoslawow (3) found, in seventeen cases of catarrhal jaundice, a sufficient amount of urea in the urine. Likewise the urea finding in cases of intermittent bilious fever deserves mention in this place. In this affection, which is almost always brought about by gallstones, the fever-producing infection is associated with the biliary stasis. Fever usually causes increased decomposition of protein, and therefore increased urea excretion. When, therefore, lower urea values were determined during the attack (4), then it was not a far cry to make the

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disturbed hepatic functions answerable for such findings. In France, Regnard's observation prevailed as a substantial support of the theory of urea formation in the liver [Charcot, Brouardel], and also Pick's slight urea values (5·34 grammes) were to him an evidence of the insufficient urea formation in the injured liver. His careful analyses did not, however, permit him to find an increased ammonia excretion, so that, in spite of the slight absolute quantity of excreted urea, this amounted to 78 per cent. of the total nitrogen, while the ammonia nitrogen showed a value of 7 per cent. of the total. Hence an insufficiency of the liver, in the sense of von Schröder's theory, is not to be considered. Therefore E. Münzer (4) explained the slight urea values during the attack of hepatic fever as an expression of an acute condition of hunger and thirst (inanition and retention, as a result of insufficient diuresis), especially as he himself, in an analogous case, saw the urea values fluctuate with the addition of food. Moreover, the lowering of the urea excretion at the time of the exacerbation of the fever has not been confirmed by other authors (4).

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E.—CHANGES OF THE BLOOD IN JAUNDICE.

1. Biliary Pigment.

The biliary pigment, after its absorption by the lymph, circulates with the blood, and is then partly deposited in the tissue cells and partly excreted in the urine. After the beginning of the biliary obstruction a certain time always elapses before absorption occurs. Meanwhile the natural excretory passages above the obstruction fill themselves to overflowing with bile. The time which expires before absorption takes place is variously estimated. Thus, Saunders found the biliary pigment in the blood of dogs two hours after ligature of the ductus choledochus, while Frerichs could discover it only in twenty-eight to forty-eight hours. Hamel has recently called attention to the point that in man jaundice is much earlier recognisable in the blood-serum than in the yellow colour of the skin or in the excretion of biliary pigment in the urine (1).

In man two to three days elapse, according to Frerichs, before the yellowing of the conjunctivæ and the occurrence of bilirubin in the urine are observed, while at other times, especially in cases of cholelithiasis, less than twenty-four hours expire [Quincke (1)]. Indeed, it is correct to assume that the intensified contractions of the gall-bladder in cases of obstruction of the ductus choledochus by stones increase the pressure in the bile-ducts, and consequently accelerate the absorption of bile.

The kidney is the real place of excretion of the biliary pigment. While it, moreover, may appear in all possible exudates and transudates, yet the real secretions—saliva, tears, gastric, intestinal, and pancreatic juices—remain free from this pigment. Hence the sweat of icterics contains, as a rule, no bilirubin; yet exceptions to this occur [Frerichs]. Thus bilirubin appears in the perspiration which is induced by pilocarpine [F. Müller, Leube, von Noorden (2)]. Mucus, likewise, contains no biliary pigment, and the sputa of icterics are, therefore, usually colourless. If, however, the processes in the lungs leading to formation of sputum are not of a secretory nature, but are transudative and exudative in character (as in œdema of the lungs, pulmonary infarcts, and pneumonia), then the ejecta contains bile (2), and, indeed, owing to the presence of oxygen in the lungs, may contain biliverdin instead of bilirubin.

That bilirubin, during its circulation, did not cause injurious effects was formerly accepted as certain. Some authors ascribe the pruritus to the deposition of pigment in the skin [Nothnagel (3)]; yet the itching of the skin is often first evident after the yellowing of the skin has existed for a long time, and disappears for the most part after the biliary obstruction is overcome [Quincke (3)], while the yellowing of the skin persists for some time. Hanot (3) even went so far as to maintain that the itching of the skin of hepatic patients could often be observed long before the appearance of jaundice, and he therefore believed that the itching was due, not to the biliary constituents, but to some still unknown substances, derived from the injured liver cells. Most writers have, however, traced this troublesome symptom to the presence of bile acids in the blood [von Leyden (3)].

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Other poisonous actions of the biliary pigment did not come under consideration until Bouchard and de Bruin called attention to such actions in a very forcible way. They injected bile into the ear vein of rabbits, and determined the lethal dose. In the same manner control animals were treated with bile which had been decolorized with charcoal. Bouchard, as also de Bruin, found that the decolorized bile had lost more than one-half of its toxicity. Pure bilirubin, administered in the same way, caused death in a dose of 5 centigrammes per kilogramme. Hence the conclusion is warranted that the toxicity of the biliary pigment exceeds that of the bile acids (4). The poisonous action extends, according to de Bruin, to the heart, kidneys, and possibly also to the central nervous system.

Pflästerer and Rywosch have raised objections to these investigations, both as regards the results and the methods of research. If it were once possible that the bilirubin had formed, with salts of calcium, insoluble compounds, which induced thrombosis of the vessels [Pflästerer], then the action of the surplus sodium hydrate solution which had served as the solvent of the bilirubin permits a wrong interpretation of the poisonous properties of the bilirubin [Rywosch]. Such poisonous action cannot be completely denied; yet Bouchard has, at all events, overrated the toxicity of bilirubin, inasmuch as this is manifest only to a slight degree, as van Ackeren (5) showed, and bears no particular relation to the constituents of the blood.

2. Bile Acids.

The conditions are otherwise in the case of the bile acids,[1] whose poisonous action on the central nervous system, heart, and blood corpuscles is so intense that the stagnated unabsorbed bile acids would kill the organism in a short time if their production continued during the disturbance of biliary outflow in the same degree as during free egress. It is to be said, however, that such is not the case.

The most discussed property of the salts of the bile acids is that of hæmolysis (6). Both with the microscope and in the test-tube this phenomenon may be easily demonstrated. However, the question is a different one when an inquiry is made whether, in cases of obstructive jaundice, blood cells are actually destroyed by the bile acids. At any rate, it is not conceivable that the decomposition is a marked one [Frerichs (6)], otherwise a hæmoglobinuria would occasionally coincide with the onset of jaundice. Where both conditions are observed together, the destruction of the blood-corpuscles is primary and the jaundice secondary, or, at the most, they are similar conditions resultant upon some poisoning, such as that with arseniuretted hydrogen, toluylendiamine, pernicious malaria, paroxysmal hæmoglobinuria, etc., or the hæmoglobinuria arises in the later stages of jaundice at a time when marked inanition and all possible varieties of still unrecognisable injuries affect the system.

[1] The literature of the toxicity of bile acids is exhaustively treated by Rywosch, Stadelmann, and A. Bickel (5), so that it is only necessary to refer to these works in this place.

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That in ordinary obstructive jaundice the bile acids are actually increased has, moreover, not been proved. As Croftan has recently shown (6), they are normally present in the blood-stream—a fact which does not occasion astonishment, since they are completely absorbed from the intestine, and appear again in the bile.

At all events, the condition of the blood in cases of uncomplicated biliary stagnation speaks against a dissolution of the erythrocytes [Cauvin]. Indeed, Becquerel and Rodier (7) emphasize the point that the blood-corpuscles may even be increased in jaundice. Von Limbeck found in two cases of very marked catarrhal jaundice no increase of the erythrocytes (4,700,000 and 5,500,000 per c.c.); in two other cases with mild jaundice he found a slight decrease in their number (3,400,000 and 3,800,000). Von Noorden reported two cases of catarrhal jaundice with 5,200,000 and 5,500,000 red blood-corpuscles.

The dry content of the blood fluctuated in three cases of severe catarrhal jaundice in women between 22 and 25 per cent. (von Noorden), while the specific gravity of the blood was estimated by Siegel in two cases as 1,057 to 1,064. Both these values are within normal variations. Because the hæmoglobin content of the investigated blood appeared to be lessened, Siegel considers the relatively high specific gravity as due to the presence of biliary constituents in the blood. This does not follow, because the bile is specifically lighter than the blood [Grawitz (8)], and hence the passage of bile into the blood cannot increase the specific gravity of the latter. Correspondingly, Hammerschlag (8) found that the density of the coloured blood-serum of icterics was not increased. According to the investigations of Grawitz (8), which comprise animal experiments also, it is true that the presence of biliary constituents in the blood exert a concentrating effect upon it, in so far as no influences arise which might bring about a complicating anæmia. In several continuously investigated cases a significant increase of the specific weight of the blood was observed coincident with an exacerbation of the jaundice, and a lowering of the same was noticed following the subsidence of the icteric symptoms.

In severe cases of jaundice certain morphological changes occur, such as a remarkably sudden thorn-apple formation of the red corpuscles and a lessening of the rouleaux formation [W. Fick, C. Gerhardt, Hofmeier), while in febrile cases a peculiar vacuole formation is occasionally observed [Weintraud]. The appearance of macro- and microcytes, and also of poikilocytes and shadows of blood-corpuscles, is reported by O. Silbermann in icterus neonatorum (9).

The resistance of the red blood-corpuscles is augmented in jaundice, and increases with the intensity of the jaundice [von Limbeck, Chanel, Viola, Maragliano]. If the icterus diminishes, the resistance again becomes normal [Maragliano]. On the basis of his experiments von Limbeck ascribes the increase of resistance to the fact that the salts of the bile acids destroy and eliminate the less resistant blood-corpuscles (10).

Von Limbeck found the number of leucocytes somewhat lower than normally (4,000 to 7,000), while Grawitz reported that he had frequently

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found them considerably increased (30,000 to 40,000) in numerous cases of uncomplicated jaundice. To a less degree Cauvin observed the same thing. F. Pick (11) noticed, in a case of intermittent bilious fever, a hyperleucocytosis limited to the time of the onset, and saw in this relation of the leucocytes a diagnostic point regarding those chronic infections of the bile-passages which run their course without pus formation.

The alkalinity of the blood is not changed [von Jaksch] or markedly increased [Brandenburg] in cases of true obstructive jaundice. The increased alkalinity may be considered an expression of the increased specific gravity of the blood. If a dissolution of red corpuscles has taken place to any considerable degree, then, according to the researches of F. Kraus (12), a lessening of the alkalinity must be expected. Such a condition has been reported only by Simnitzki and Radoslawow.

According to the results of blood analysis it is, moreover, absolutely uncertain whether hæmolysis by bile acids generally occurs in cases of uncomplicated biliary stasis, for their concentration in the blood is probably always too small to bring about such a condition. At all events, the conclusions which Nothnagel deduces (12) are much too comprehensive. In catarrhal jaundice red blood-corpuscles are destroyed by the bile acids, as a consequence of which we observe a diminishing of the oxygen-carrying power of the blood, a lessening of the oxidation and of the general metabolism, and a lowering of the body temperature in jaundice. In the whole series of the above assumptions only this can be acknowledged as a fact: that about one-third of the patients with catarrhal jaundice have a subnormal body temperature. Even if this point is actually dependent on the presence of the bile acids [Röhrig], then the paralyzing influence of the bile acids on the vascular system should be indicated rather than their poisonous action on the red blood-corpuscles.

Among the actions of the bile acids upon the cardio-vascular system the slowing of the heart-beat is best known, but its pathogenesis is very complicated. Röhrig (13), who first observed that the bile acids, and not other constituents of the bile circulating in the blood, induced a slowing of the pulse, regarded this action as due to the direct effect of the bile acids on the heart. The majority of writers agree with him, whether they, like he, assumed the direct point of attack of the bile acids to be the intracardiac ganglia [Wickham Legg] or the heart muscle itself [J. Ranke, Schack]. Traube, Feltz and Ritter, and Leyden believed that the bile acids indirectly weaken the heart muscle through an alteration in the blood, which affects the nutrition and functional activity of the heart. Likewise is explained the view of the clinicians, Ewald, Grob, Riegel, Laveran, and Teissier, that the bradycardia observed in jaundice is due to the action of the bile acids upon the heart (13).

On the contrary, it has, however, been shown by Löwit, A. Biedl and R. Kraus, and others, that the bile which is brought to the brain by the blood calls forth marked stimulative effects, and as a result is in position to cause changes in the rhythm of the heart-beat. Also Spalitta, on the ground of his investigations, has come to the conclusion that the salts of the bile acids stimulate the inhibitory fibres of the vagus nerve. Therefore the observation of Weintraud that the slowing of the pulse in a case

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of catarrhal jaundice was promptly overcome by an injection of atropin would indicate that the bradycardia in jaundice is dependent on a central stimulation of the inhibitory mechanism.

Exact analysis of the process has recently lead Brandenburg to the view that it cannot be so much a question of direct stimulation of the vagus centre as, rather, one of vagus stimulation arising reflexly from excitement of the intrinsic nerves of the heart. To this is united, as a result of long-continued action of the salts of the bile acids, a gradually developing injury of the sensitive muscle cells at the mouths of the large veins, from which point the stimulative effects pass to the lower-lying parts of the heart.

According to von Noorden, this bradycardia has the peculiarity that it accompanies a large, soft, almost dicrotic pulse, while ordinarily in cases of bradycardia a small or large pulse, hard and of high tension, is the general rule. This agrees with the observation of Löwit, who always observed, in the first place, a lowering of the blood-pressure following injection of the sodium salts of the bile acids into the blood-current towards the heart. Likewise this harmonizes with the data of Rywosch regarding the paralyzing effect of the bile acids upon the vessels, which effect appeared in the animal experiments independently of the slowing of the pulse. This has also been recently confirmed by Sorrentino. The sphygmographic observations of Marey and Kleinpetter show, on the other hand, an increase of blood-pressure in jaundice.

Phenomena of Agglutination.

A series of observations are known which attribute to the blood-serum of liver diseases, and especially in such as are accompanied by biliary stasis, an agglutinating action on the *Bacillus typhosus* (15). In one case the course of the agglutination points directly to the causal relation of the biliary retention [L. Langstein], inasmuch as the reaction was positive at the time when an absolute biliary stasis occurred. As soon as a slight amount of bile mixed with the intestinal contents, although the jaundice was externally unchanged, the agglutinating power of the blood-serum was lost.

This observation finds its experimental analogy in the investigations of P. Koehler (15), who furnished the proof that injection of taurocholic acid into the blood-current and the ligature of the ductus choledochus in animals gave the blood-serum agglutinating powers. The soundness of these experiments, as well as of the results obtained in the investigations of the serum of icterics, has been doubted. Königstein found the agglutinating value of the blood of icterics to be no higher than that of healthy men, and his view has this much in its favour: that in cases of the occasional occurrence of the Gruber-Widal reaction during febrile jaundice there is a question of a group agglutination—that is, in other words, that the cause of the cholangitis to which the jaundice is due may not be very far removed from the colon group. Steinberg's investigations show, moreover, that a biliary stasis of a marked degree may exist without the blood-serum acquiring the property of agglutinating the *Bacillus typhosus*.

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F.—REACTION OF BILIARY STASIS UPON THE CENTRAL NERVOUS SYSTEM.

Experimental pathology has studied the poisonous effect of the bile acids upon the central nervous system with especial care. However, the many contradictions which characterize even the results of the investigations in this field have consequently conduced to a marked confusion of views, so that to-day no explanation can be deduced from the animal experiments regarding the peculiarly severe conditions which occasionally arise quite spontaneously in diseases of the liver.

After subcutaneous or intravenous injection of bile acids into animals death follows either with convulsions (16) or with the intervention of a comatose state [Röhrig, Rywosch (16)]. Fatigue and weakness follow small non-lethal doses of the bile acids, a condition which the physician sees in cases of jaundice. On the other hand, it is absolutely uncertain whether also the known symptom-complex of cholæmia (which appears in the course of severe jaundice, and after the intervention of marked periods of excitement, raving delirium, spasms in isolated groups of muscles, and general convulsions, leads to death in coma) has its analogy in the animal investigations, and may be interpreted as being an intoxication with bile acids [Stadelmann (16)]. As a matter of fact, it is in these cases of cholæmia that the amount of bile acids in the urine is lessened, and also not much increased in the blood; while, according to the previous animal experiments, large amounts of these acids must circulate in the blood. Biedl and R. Kraus (17) have recently succeeded —by the use of a special method of introducing into the body relatively much smaller doses of the bile acids—in producing marked stimulation of the central nervous system with such characteristic brain symptoms that there can be no further doubt that the pathogenesis of cholæmia is traceable to a poisoning of the brain with bile acids. The method of subdural injection which these authors selected has, however, been criticised from the pharmacological aspect by Bruns (17) as not being suitable to the study of the general action of a substance circulating in the blood. Moreover, the suspicion has, at the same time, been expressed that the severe brain phenomena are the result of a local stimulative action on certain centres, and not, as Biedl and Kraus maintained, due to an elective action of the bile acids on the ganglion cells.

This same criticism has likewise been applied to the technique of the experiments of A. Bickel (17), who systematically investigated the action of the biliary constituents and of the products of the decomposition of protein on the central nervous system by spreading the substance to be studied upon the exposed surface of the brain. Likewise in these experiments the fact is evident that the substances used in this method of research show quite a different action than when injected into the animal subcutaneously or intravenously. At the same time, the point must be considered that a large number of substances (besides the bile and the salts of the bile acids), especially the various salts of ammonium, induce a practically identical action if applied in the above manner. Hence Bickel, an adherent of the toxic conception of cholæmia, is far

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from ascribing to the biliary constituents an exclusive meaning as regards this symptom-complex. On the contrary, he inclines toward the view that in many cases of cholæmia, as observed in acute yellow atrophy of the liver and in cirrhosis, the overloading of the tissues with ammonium salts may have a causal relation, and cites in evidence the high ammonia values which have been found in the urine in individual cases [Weintraud, E. Münzer, Bonani (18)], as also the marked ammonia content of the brain, which is observed in animals after removal of the liver [Salaskin, Nencki, and Pawlow]. The cholæmic toxic phenomena observed in dogs with an Eck's fistula have been ascribed to the action fo carbamic acid (18).

Biliary pigment and also bile acids have been demonstrated in the spinal fluid obtained by lumbar puncture [A. Gilbert and J. Castaigne (18)].

Cholesterin.

According to a view at present abandoned, one of the most essential functions of the liver was to withdraw from the blood the cholesterin which was given to the blood by the nerve tissues, and to excrete it with the bile. On this basis arose the theory which Flint, and following him Tincelen, Pages, and K. Müller (19) supported, according to which a disturbance of the above-mentioned function of the liver, or, indeed, an obstruction of the biliary ducts, could bring about an accumulation of cholesterin in the blood and the resultant severe symptoms of cholæmia. Flint based his view on the cholesterin content of the blood. He observed hypernormal amounts in the blood of patients suffering with cholæmic conditions as a result of liver disease. The experimental basis of Pages and K. Müller is not free from objections, inasmuch as the former introduced into the blood-current only cholesterin in a partly undissolved condition in an amygdalin soap solution, while the latter used as a carrier glycerin, which itself produces toxic effects. Rywosch (5), as well as Feltz and Ritter (13), found cholesterin to be nontoxic.

Neither the liver cell is regarded as the place of formation of cholesterin, nor the liver itself as the place of excretion of the cholesterin, which is constantly present in the blood. Rather, the cholesterin of the bile may be formed by the breaking down of the epithelium of the bile-ducts, and perhaps also by the decomposition of the liver cells, and correspondingly it may be increased in catarrhal conditions of the bile-ducts according to the extent of the desquamation. Its excretion with the bile has absolutely nothing to do with its concentration in the blood, in which it circulates in the form of fatty acid esters (20).

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G.—INFLUENCE OF STAGNATION OF BILE ON THE COMPOSITION OF THE URINE.

1. The *quantity of urine* is usually lowered at the beginning of the biliary obstruction—as, for instance, in catarrhal jaundice. This may be sufficiently explained by the lessened general nutrition or by the water intake. In fully developed cases irregularities of the urinary excretion are not observed. After the jaundice has subsided, and also after the obstruction is overcome, polyuria and polydipsia usually appear. Amounts of 2,500 to 3,500 c.c. are, even in women, not unusual during the early days of convalescence [Gilbert and Castaigne (1)].

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2. *Total nitrogen* (see protein decomposition, urea, ammonia, leucin and tyrosin).

3. *Uric Acid and Purin Bases.*—The liver does not occupy a special place in the nuclein metabolism of man and mammalians, hence the formation of uric acid is not imposed on it. Therefore the excretion of purin bodies is also, in cases of liver disease, shown to be actually dependent on the nuclein content of the food in so far as there occurs no increased decomposition of protein, which leads to excretion of endogenous purin in the urine. Such decomposition does not appear in cases of ordinary obstructive jaundice, yet the amounts of uric acid which J. Jacobs (1) recorded in three cases of biliary stasis (0·917 to 1·00 to 1·466 grammes per diem) seem quite considerable.

Von Noorden, on the other hand, obtained in four cases only 0·56 to 0·79 gramme per diem, while Pott found in a case complicated with carcinoma 0·8 to 1·0 gramme. In the above-cited case of complete obstruction of the bile-duct by carcinoma the amount of excreted uric acid was 0·64 to 0·69 gramme, in which case the nitrogenous equilibrium was controlled by the intake and output, and a protein decomposition of about 90 grammes per diem was observed. By administration of 10 grammes of nucleinic acid, the excretion of uric acid increased to 1·63 to 1·68 grammes without the nitrogenous equilibrium being disturbed (as there appeared on the days of the experiment a retention of nitrogen). Such results may likewise be observed in healthy subjects after the same administration of nucleinic acid.

4. *Hippuric Acid.*—Hippuric acid may be increased in the urine of patients with hepatic disease. Kühne states that icteric men and dogs do not excrete administered benzoic acid as hippuric acid, but as benzoates. He supposed that insufficient glycocoll was formed during jaundice, and therefore the synthesis of hippuric acid in the organism did not take place. Neukomm, Schultzen, and Baumstock (2), working with improved methods, were unable to confirm Kühne's observations. In the case of an icteric patient who excreted 0·353 gramme of hippuric acid per diem, 5 grammes of sodium benzoate increased the amount of hippuric acid excreted in twenty-four hours to 4·64 and 5·144 grammes (0·49 and 0·47 gramme being excreted on the following days). Also, in healthy subjects, the increase of hippuric acid following administration of such amounts of benzoic acid often reaches only 75 per cent. of the expected yield (calculated from the benzoic acid) [Weintraud].

Zimmermann (3) thought that a deficiency of glycocoll must arise after diverting the flow of bile externally, as in the case of a biliary fistula. As a matter of fact, he did find in such a case that, after the administration of 5 grammes of sidonal, the urine was absolutely free from hippuric acid, while benzoic acid was abundantly excreted (the quinic acid which is contained in the sidonal is converted into benzoic acid in the organism).

The fact that a few days later—after administration of 5 grammes of sodium benzoate—a copious excretion of hippuric acid occurred in the urine, although at that time neither bile nor a derivative of biliary pigment could be detected in the fæces by any known reaction, should have made him more careful in the interpretation of his observation. At any

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rate, the conclusion is not warranted that the liver, as the source of glycocholates, serves as the only source of glycocoll in the system. If this were so, then, as S. Rosenberg (3) so aptly remarks, appreciable amounts of hippuric acid could not appear in the urine after feeding with benzoic acid, since dog's bile only contains traces of glycocholic acid. However, even after diverting the flow of bile externally, and preventing any absorption of the outflowing bile, considerable amounts of hippuric acid are found in the urine of dogs on the administration of benzoic acid. The system has at its disposal large amounts of glycocoll, which arise from the decomposition of the protein, and whose synthesis with benzoic acid is not a function of the liver, but of the kidney [Bunge and Schmiedeberg].

5. *Bilirubin* and hydrobilirubin in the urine (see p. 244).

6. *Bile acids* (see p. 251).

7. *Oxalic Acid.*—Schultzen (4) first recorded the presence of large amounts of oxalic acid in the urine in cases of biliary stasis. On the basis of 0·07 gramme as the normal amount, his values in jaundice reach 0·5 gramme per diem. Fürbinger (4) reports the same figures in jaundice, obtaining in the healthy individual only 0·02 gramme in the daily urine. Mohr and Salomon did not observe an increased excretion of oxalic acid, their figures obtained from icteric patients agreeing with those of normal adults (*cf.* Oxaluria).

8. *Fatty Acids.*—F. Blumenthal (5) reported an increased excretion of fatty acids in the urine of icterics.

9. *Sulphuric Acid and Neutral Sulphur.*—The excretion of total sulphur in the urine depends on the extent of protein decomposition, and is correspondingly increased in cases in which toxic decomposition of protein takes place [R. Schmidt (6)].

The amount of conjugated sulphuric acid in the urine depends, according to the accepted view, on the extent to which the aromatic conjugates are formed in the system. This point is fully discussed in the section on Intestinal Putrefaction in Cases of Biliary Obstruction. In jaundice an increase of conjugated sulphuric acid in the urine is the rule. Nothing is known regarding disturbances of this conjugation, which seem to be localized in the liver [G. Embden and K. Glaessner (6)].

The question has been discussed by Eiger and Hopadze (6) whether the aromatic compounds formed in the system are diminished in amount and destroyed under normal conditions of hepatic activity, and whether, in cases of disturbance of the functions of the liver, these compounds are obviously increased and placed at the disposal of the liver for conjugation with sulphuric acid. The subject is more important in its relation to cases of disease of the hepatic parenchyma than to simple biliary stasis. The ethereal sulphuric acids are most frequently, both absolutely and relatively, increased in atrophic cirrhosis of the liver, and most markedly in tumours of the liver.

In normal urine 14 to 25 per cent. of the total sulphur is present as the so-called neutral sulphur. The easily oxidizable portion of this must arise from the sulphocyanate of the saliva, and from other partly unknown substances, while the remainder is regarded—in part, at least—as a

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derivative of the taurin of the bile [Lépine (6)]. This latter bears, in the nomenclature of the French physiologists, the name " biliary sulphur of the urine."

Lépine found, in incipient cases of obstructive jaundice in animals and in man, the biliary sulphur absolutely and relatively increased as regards the oxidized sulphur (up to 30 to 43 per cent. of the total sulphur). After a few days of the biliary obstruction, the sulphur became approximately normal, and after long continuance of the disturbance showed a decrease.

Regarding the fate of taurin and the origin of the neutral sulphur in the body, the with difficulty oxidizable neutral sulphur cannot yet be regarded as the amount of formed, absorbed, and decomposed taurocholic acid. For instance, it has been shown that both components of the neutral sulphur vary within the widest limits in spite of feeding with the same amounts of food, and notwithstanding the same external relations of the animals used in the experiments, so that the special relation of the with difficulty oxidizable sulphur to taurin becomes rather doubtful [Benedict]. Nevertheless, attention must be called to the fact that the early increase and later decrease of the neutral sulphur described by Lépine is very comparable to the view which we must take regarding the process of the formation of biliary acids in jaundice.

The following example, selected from Lépine's work on cholelithiasis, illustrates the course of excretion of neutral sulphur in jaundice:

May 2: light jaundice. „ 3: light jaundice; neutral sulphur = 31 per cent. „ 6: sudden increase of jaundice. „ 7: marked jaundice; neutral sulphur = 43 per cent. „ 10: marked jaundice; neutral sulphur = 20 per cent.	Total sulphur = 100.

F. Müller (6), who studied a case of jaundice from gall-stones of somewhat long standing, found on three days the values of the neutral sulphur to be 22·9, 15·7, and 10·7 per cent. of the total sulphur. Later in the same case, but with different diet, the values were 19·2 and 17·4 per cent. In a case of carcinoma of the stomach and liver, accompanied by jaundice, the findings were 29·0, 21·1, and 16·1 per cent. These figures confirm Lépine's idea that the neutral sulphur diminishes the longer the jaundice continues.

On the other hand, a marked decrease, and even a lowering of the normal values, should be expected in chronic obstructive jaundice, provided the assumption is correct that in cases of disturbed outflow of bile into the intestine the production of biliary acids is markedly reduced by the interruption of the circulation of bile acids. Since this is not observed, the relation of the hardly oxidizable sulphur to taurocholic acid must be re-investigated before an opinion on the formation of bile acids can be based on the excretion of neutral sulphur. Hence it does not follow that Schmidt (6) should assume that the production of bile acids, even in long-continued jaundice, suffers no reduction, because he but rarely found high values for the neutral sulphur in his case of jaundice. According to Benedict (6), a portion of the non-oxidized sulphur compounds, which may be excreted in increased amounts as a result of toxic

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action on the protein constituents of the body, are to be regarded as intermediary bodies, which resist the further oxidation to sulphuric acid. Corresponding to their presence in the bile [Bial], conjugated glycuronic acids are regularly observed in the urine in cases of biliary obstruction [van Leersum (6)].

10. *Albumin* is found in traces in most icteric urines, but only seldom in large amounts. The albuminuria of jaundice is ascribed to the injury of the renal epithelium by the passage through it of abnormal constituents of the blood, such as biliary pigment and biliary acids. It is accompanied by the appearance of clear yellow hyaline casts, which are often numerous in relation to the very slight albuminuria [Nothnagel (7)]. As an analogy to this, pure cylindruria may occur in cases of artificially produced biliary stasis [P. S. Wallerstein (7)]. In two cases of simple catarrhal jaundice von Noorden (7) found much nucleo-albumin in the urine.

11. The *molecular concentration* of the urine undergoes no essential change in cases of simple obstructive jaundice [Ferrannini (8)].

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II.—INFLUENCE OF CIRRHOSIS OF THE LIVER ON THE METABOLISM.

The conception of the unity of the cirrhoses, which is justified from the anatomical standpoint, seems to be overthrown by the findings of the pathology of metabolism, inasmuch as entirely different disturbances of metabolism, both as regards their form and extent, arise in the various clinical types of the disease.

One class of disturbances has its origin in the injury to the circulation of the blood. The stagnation in the portal circulation affects the digestive organs and disturbs their function. The liver, likewise, is more or less shut off from the portal circulation, and resultant phenomena arise.

A second series of disturbances depends on functional changes in the liver cell—whether the cell is primarily affected or secondarily influenced by conditions such as biliary stasis as a result of toxic or infectious cholangitis, or of proliferation of connective tissue.

The typical cases of atrophic (Laennec's) cirrhosis and of biliary (Hanot's) cirrhosis are, in these respects, opposed to one another to a certain extent.

A.—INFLUENCE ON THE GENERAL METABOLISM AND THE NUTRITION.

So far as the calorie consumption has been investigated in hepatic cirrhosis, there are no signs that it is otherwise than would be expected from the general state of nutrition and from the external conditions [Bierens de Haan (1)]. However, it is well established that patients who have for a long time maintained their nutrition at a useful level suddenly manifest a marasmus which is severe, and, once begun, is usually rapidly progressive. The fat and muscle disappear, and the body-weight diminishes unless the onset of œdema compensates for such loss. This marasmus is in reality induced by lack of food, and not by the insufficiency of any hepatic function.

The disease in its further course almost always gives rise to dyspeptic disturbances, as a result of slowing of the circulation and overloading of the digestive organs with blood. The tendency in these cases to gastric and intestinal hæmorrhage and to diarrhœa is well known. If such factors arise, then the food intake immediately falls. Likewise, judged from the acute exacerbations, digestive disturbances are seldom lacking, although they may consist only in lessened appetite and uncomfortable feeling after eating. In other cases there arises, as a result of the action of the same poison (alcohol), a gastric disorder as an independent and important complication of the atrophic process in the liver.

The individual disturbances are not similarly grouped in each case. However, they always interpose an obstacle to the maintenance of the nutrition. The small food intake of patients with cirrhosis of the liver and with an already appearing marasmus affords a ready explanation

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of the loss of weight. Von Noorden (1) has recorded the amount of food taken by three such patients as equal to 10, 14, and 19 calories per kilogramme and per day—that is, one-half to one-third of the actual need.

The satisfactory course of those cases in which the severe reaction of the portal stasis upon the functional activity of the digestive organs has been obviated by Talma's operation demonstrates again very clearly that the disturbed circulation of the blood, and not the insufficiency of the hepatic function, has brought the patient to the edge of the grave. The consumption of food, as a result of returning appetite, leads to an increase in body-weight, which differs in no way from that of ordinary convalescence, and shows also that the changes in the liver exert in themselves no influence on the state of nutrition in cases of atrophic (Laennec's) cirrhosis of the liver.

B.—INFLUENCE ON THE METABOLISM OF PROTEIN.

In considering the question whether cirrhosis of the liver furnishes the occasion for production of protoplasmic poisons, and hence stimulates pathologic decomposition of protein, the diversity of the types of the disease must be remembered. This point shows itself so markedly in this connection that individual investigators speak of a basic difference. Thus G. Ascoli (1) compared the metabolic balances of two patients, with the following results: while one case (hypertrophic cirrhosis of Laennec) constantly showed a marked positive nitrogen balance, so that in two seven-day periods an average amount of 0·3 and 6·5 grammes nitrogen were retained on a calorie addition of 48 to 60 calories per kilogramme a day, a case of Hanot's cirrhosis showed, in direct contradiction, a striking tendency to loss of nitrogen, which led in two seven-day periods to an average loss of 7·4 and 1·3 grammes of nitrogen on a daily addition of 28 to 57 calories. Corresponding to this comparison, Bierens de Haan found a pathologically increased decomposition of protein only in one case of cirrhosis of the liver accompanied by chronic jaundice, while in all (4) his other cases nitrogenous equilibrium or nitrogenous retention was present.

So far as the experience of others regarding the nitrogenous decomposition in atrophic cirrhosis is concerned, it agrees fully with the above findings. Transitory, but constantly slight, losses of albumin are found in only one of Fawitzki's (2) cases, while the five remaining patients in different stages of cirrhosis retained nitrogen on an average diet. Similar findings were noted in the investigations of Calabrese (2), and of Marischler and Ozarkiewicz (2), upon atrophic cirrhosis. In these cases quite a marked retention of nitrogen was reported, yet in the interpretation of these figures an accompanying formation of ascites must be considered. The same thing holds for a case of atrophic cirrhosis reported by E. Münzer (2), in which the nitrogen intake with the food and the output in the urine (without reference to the nitrogen excretion in the fæces) were observed. His results show a retention of 56 grammes of nitrogen

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in seven days, but along with this an extensive ascites was noted. Positive nitrogen balances are likewise shown in his two other cases, which are regarded as Hanot's type of the disease, since they ran their course as hypertrophic cirrhosis with jaundice. This finding contradicts the above-mentioned observation of Ascoli, who doubts, in this connection, that Münzer's cases were really types of biliary cirrhosis. From the ease with which continuous loss of protein occurred in his case of Hanot's cirrhosis on a diet with moderate and even excessive calorie value, and the fact that even by restriction of the diet in cases of inanition the excretion of nitrogen remains at a high level, Ascoli concludes that a toxic decomposition of protein characterizes Hanot's as opposed to Laennec's cirrhosis.

Without further discussion, the nitrogen retention observed in the positive balances of Marischler and Ozarkiewicz cannot be regarded as an increase of protein in the sense of a deposition of protein in the tissues. At any rate, a part of the retained nitrogen is not included in the accumulating ascites, since Marischler and Ozarkiewicz even then found an excess of 11 grammes of nitrogen in eleven days after allowance for the nitrogen of the ascitic fluid. Likewise the chloride retention was shown to exceed that of the ascites fluid. Does this increase of nitrogen mean a corresponding increase of protein in the tissues? Such an assumption seems undoubtedly somewhat forced in the case of an intensely sick patient. The nitrogen retention which is observed in cachectic conditions, oftentimes in astonishing amounts, has justly received the interpretation that in this case the inability to split up the ingested protein and to excrete the nitrogen has led to an accumulation of protein refuse [E. Schmoll, Schöpp, von Moraczewski (3)].

Marischler and Ozarkiewicz also adopt this explanation, which appears so much the more plausible inasmuch as a corresponding phosphorus retention does not run parallel to the nitrogen and chlorine retention. Such a nitrogen retention, which arises from a functional deficiency of the system, is naturally to be valued somewhat differently than a nitrogen deposition in the sense of incorporation of protein in the system. Unfortunately, we are still lacking sufficiently exact evidence to enable us to differentiate them. The impression obtained from the general nutrition of the patient must be the decisive point for some time to come.

The relations of the nitrogenous equilibrium appear, however, especially complicated when, along with the cachexia, the accumulation and, occasionally, the rapid removal of a peritoneal exudate by puncture play their part. A new factor thus appears. In other words, the system day by day utilizes protein material in the formation of the ascites. To what extent this occurs may be ascertained in part by the removal and analysis of the ascitic fluid after a series of days, calculating therefrom the daily average. The view that in the first days no other material, whether it be poorer in protein and richer in salt, or *vice versa*, is used in the formation of the exudate than in the later periods is not yet sufficiently proved.

The question now arises—namely, whence comes the material out of which the ascitic fluid is formed? Is the food protein retained in its

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formation, or is it completely destroyed, and the albumin of the ascitic fluid increased at the expense of the tissue protein ?

The determination of the metabolism in ascites, the comparison of the periods before abdominal puncture and during the period of reaccumulation of fluid, the comparison of the ascitic fluids which have collected concomitantly with food intakes, varying in their protein content, have given no definite answer to the problem [Schubert, Marischler and Ozarkiewicz, O. Schulz and L. R. Müller]. Indeed, the question should not be so put. Circulating protein, in the sense of Voit's teaching, is no longer recognised. All protein which is broken down in the system is previously assimilated by the protoplasm of the body cell. Hence the same must be true of the protein which is excreted from the tissue fluids into the peritoneal cavity in ascites. Schulz and Müller (4) found that an abundant addition of protein to the dietary did not increase the absolute amount of the nitrogen daily excreted into the peritoneal cavity. Similarly, a diet poor in protein did not diminish the loss of nitrogen observed in the ascites. Indeed, the percentage nitrogen content of transudates runs parallel to the nitrogen content of the food, for the extent of the transudation stream is lessened by a diet rich in protein, and increased by one poor in protein, the effect on the nitrogenous equilibrium thus being equalized.

The usually cited view that the protein decomposition is lessened (hypo-azoturia) in cases of cirrhosis of the liver, as generally in all liver diseases, may be mentioned in this place, along with the figures obtained by exact quantitative metabolic investigations regarding the nitrogen exchange of the cirrhotic patient, more as an historical reminiscence than otherwise.

The most notable adherents of this view are Brouardel and Charcot (5), who found low urea values in the urine by the use of Liebig's titration method, and concluded therefrom that the urea formation is lessened because the urea-forming organ, the liver, is diseased. As a matter of fact, Liebig's method gives absolutely no information as to the urea of the urine, only determining its total nitrogen. For that reason the low figures of these authors only show the protein decomposition, and do not indicate any specific work of the liver cells. The reason for the slight protein decomposition (often only 20 to 30 grammes per diem) which Brouardel (5), Charcot (5), Kirikow, and others report lies manifestly in the protracted state of inanition of the patient. In the same way in Stadelmann's cases, low nitrogen values were constantly accompanied by very slight NaCl excretion (a sure sign of inanition). Unfortunately, in all these cases only the urine was analyzed, the composition of the food and fæces not being determined.

C.—INFLUENCE ON THE DIGESTIVE ORGANS.

1. Gastric Digestion.

Rendu (6) asserted that the secretion of gastric juice was markedly reduced in cases of cirrhosis of the liver. Von Noorden (6) found in four cases of pronounced alcoholic cirrhosis with ascites, twice a normal, and

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twice a decreased, amount of hydrochloric acid. In six cases of hypertrophic icteric cirrhosis, Kirikow (5) observed diminished acidity, even a disappearance of free hydrochloric acid. On the other hand, Hayem and others (6) noted the condition of hyperchlorhydria in hypertrophic icteric cirrhosis as opposed to atrophic cirrhosis. According to Rendu, the gastric juice of the cirrhotic patient contains less pepsin than normal.

2. Biliary Secretion.

The secretion of bile cannot be directly measured in cases of hepatic cirrhosis. It varies in the different types of the disease, and the variation may be an actual differential point of the several types. In the true alcoholic (Laennec's) cirrhosis marked stagnation of bile is very rare, and always accidental. In most cases there is only a very dirty-yellow colour of the skin. The absorption of bilirubin is sufficiently intense to tinge susceptible tissues, but its concentration in the blood does not suffice to cause a transference of the biliary pigment to the urine. Correspondingly, the fæces remain dark-coloured and poor in fat.

In biliary (Hanot's) cirrhosis, the passage of biliary pigment into the blood betrays itself in the pronounced intense jaundice. The urine also contains bilirubin in abundance. In spite of this, the outflow of bile into the intestine is, in these cases, not interrupted, the fæces are not decolorized, but, on the contrary, in a number of cases are often coloured markedly brown by pigment—a characteristic which should be well remembered.

The slight jaundice appears to be unaffected by the intrahepatic biliary stasis, while the pronounced jaundice is mechanically conditional upon it. In cases of atrophic cirrhosis, the anatomically easily intelligible involvement of individual portions of the liver may be accountable for the stagnation, while in cases of biliary cirrhosis cholangitis may be blamed for that condition.

Less clear is the genesis of hydrobilinuria, which is so very frequent and pronounced in cases of hepatic cirrhosis. It stands in a certain contrast to jaundice, and is slight or absolutely absent if in the first place abundant biliary pigment appears in the urine. It is found most often, and in the most marked degree, in atrophic cirrhosis.

There is no sufficient basis for the assumption that in these cases urobilin is formed in large amounts elsewhere than in the intestine. It is obvious that the liver, in spite of the intrahepatic biliary stasis and absorption, still furnishes the intestine with abundant biliary pigment, so that urobilin is there formed and absorbed. If, however, the liver lacks the power of reconverting the urobilin into bilirubin, then the former also appears in the bile, and is again passed into the intestine, from whence it is easily absorbed, and is excreted in the urine in large amounts. Similarly, blood-serum and transudates often contain urobilin.

3. Absorption of Food.

As has been said, the outflow of bile into the intestine is maintained to such an extent in cases of pure uncomplicated cirrhosis of the liver

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that the fæces retain their normal colour. Hence the injurious effects are slight as regards absorption from the bowel.

In F. Müller's (7) cases the absorption suffered only when the stools were diarrhœic, which is certainly not an unusual finding in cirrhosis. Likewise the tables of Fawitzki and others (7) show that diarrhœa occurred whenever a marked loss (up to 15 to 20 per cent. of the intake) of nitrogen in the fæces was observed; in other respects the utilization of the food was approximately normal.

Schubert (7) found in three cases an average nitrogen loss of the fæces of 1·7, 2·534, and 1·162 grammes of nitrogen. Within the same limits fluctuate the figures of Marischler and Ozarkiewicz. Münzer (7), without estimating the fæcal nitrogen, drew the conclusion, from the slight excretion of nitrogen in the urine, that absorption of the ingested food was affected—at least, in certain stages of cirrhosis of the liver. This conclusion is less subject to generalization, as the figures given for the weight of the evacuated fæces (500 to 600 grammes) warrants the assumption of an existing diarrhœa. F. Schupfer (17) also speaks of lessened utilization of food in cirrhosis of the liver.

D.—INFLUENCE ON THE BLOOD.

Maragliano (8) reported that the power of resistance of the red blood-corpuscles was lessened in cirrhosis of the liver. This statement is based on test-tube experiments, which do not prove that in the circulating blood of cirrhotic patients an increased breaking-down of erythrocytes takes place. Some observations, however, agree very well with this assumption. In the first place, there is the marked secretion of bilirubin; secondly, there is the diminished alkalinity of the blood [von Jaksch]; and, finally, there is the undoubted hydræmia of the blood, which never is lacking in far-advanced cases. The number of erythrocytes is always more or less diminished in such cases [S. Rosenstein and Wjalew], and the hæmoglobin content of the blood is decreased. The severe anæmia described by Hocke (two cases) is, however, rare. The considerable decrease in the nitrogen content of the red blood-corpuscles shown in Hocke's experiments is curious, inasmuch as an increase in the nitrogen content of the corpuscles is present (8).

The leucocytes are increased in the majority of cases of Hanot's cirrhosis [Cauvin]—9,000 to 16,000 leucocytes [Wjalew], 8,800 to 21,800 [Hanot and Meunier (8)]. In cases in which febrile infection plays a rôle, as is usual in biliary cirrhosis, a leucocytosis is not remarkable. Hence one is not at all astonished to find that the hyperleucocytosis is oftentimes lacking [Popow (8)].

Nothing is known of any special chemical characteristics of the blood. The occurrence of a marked increase of non-protein nitrogen in a case of thrombosis of the portal vein deserves mention in this place. While 2 to 16 per cent. of the total nitrogen of the blood normally found exists in combination with non-protein bodies, in this case, where the blood flowing away from the intestine could not circulate in the liver, the amount of such nitrogen reached 42 per cent. of the total nitrogen [J. Joachim

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(4)]. Schulz and Müller (4) also found that 14 to 18 per cent. of the total nitrogen of the ascitic fluid in a case of thrombosis of the portal vein was in a non-albuminous form.

E.—INFLUENCE ON THE URINE.

1. Quantity.

The amount of urine varies considerably in the course of the disease. Besides being dependent on the amount of water intake, it is influenced by the following factors—namely, increase or decrease of ascites, stagnation in the region of the vena cava, and accompanying diarrhœa. The interrelations of these conditions are clear, and need no elaboration.

French writers mention retarded excretion of urine ("opsiuria") in cases of cirrhosis [A. Gilbert and Lereboullet, Lecerf (9)]. Normally, an increased excretion of urine is observed in the first hours after eating. In cirrhosis this outflow of urine after a meal is retarded; this has been determined by fractional collection and measurement of the urine.

2. Nitrogen-containing Constituents.

The *total nitrogen* as a measure of the protein decomposition has been considered already. The question of the nitrogen-containing substances in the urine of the cirrhotic patient is of great interest. Much more plausible in cases of cirrhosis than in obstructive jaundice is the idea that in the former instance the liver, with its injured parenchyma, is unable to complete the resynthesis of the protein derivatives, and, as a result, liberates half-formed metabolic products into the circulation.

Ammonia.—In view of the prevailing conception that the formation of urea from ammonia is largely localized in the liver, it is important to inquire whether, in diffuse disease of this organ, the ammonia is increased at the expense of the urea. In the sense of von Schröder-Schmiedeberg's theory, an indication of a disturbance of the urea formation in the liver would thus be given.

Numerous clinical observations signify something of this sort. The ammonia values in cases of cirrhosis are remarkably high. Hallervorden and others (10) obtained high values in comparison with the total nitrogen decomposition. For example, Mörner and Sjöquist in one case found the total daily nitrogen to be 20·748 grammes, the total twenty-four hours' ammonia to be 2·4 grammes, the ammonia nitrogen being 9·5 per cent. of the total nitrogen, and the urea nitrogen 84·6 per cent. In five cases Fawitzki calculated the ammonia nitrogen, on the basis of 100 parts of total nitrogen, as follows: 17·5, 10·7, 7·6, 10·0, 9·8 parts. Gumlich found 5·7 grammes total nitrogen and 0·86 gramme ammonia, the ammonia making up 12·3 per cent., and the urea 70 per cent., of the total nitrogen. In von Noorden's cases the ammonia nitrogen reached 8·5 to 12·6 per cent. of the total nitrogen, the normal value being 3 to 5 per cent. One of Schubert's cases yielded ammonia nitrogen constantly over 10 per cent. of that of total nitrogen (in one day up to 18·17 per cent.). Such high values are, however, far from being usual. Indeed, in the cases of

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Stadelmann and Weintraud there were many which showed absolutely no increase in the ammonia output. The highest values, markedly increased in comparison with those of the preceding day, were estimated *sub finem vitæ*—that is, after the appearance of cholæmic symptoms.

The *urea* content of the urine has been less often determined. The relative figures found for urea are all below those of the normal value—90 per cent. of the total nitrogen [Landau (10)]. In Fawitzki's six cases the average urea nitrogen values of long series of observations were found to be 78·9, 88·4, 87·1, 89·2, 88·8, 89·0 per cent. of the total nitrogen; in Münzer's cases, 82·2 and 86·7 per cent.; in Mörner and Sjöquist's, 84·6, 73·2, and 84·9 per cent. In von Noorden's observations, however, the values were 77 to 79 per cent., and in Gumlich's cases only 70 to 77·6 per cent. Urea given *per os* to such patients is promptly excreted [Setti and De Stefanio (10)].

When the absolute amount of excreted urea is considered, then these values, even in advanced cases of cirrhosis, are by no means small [Ajello and Solaro]. Mörner and Sjöquist's patient excreted 2·4 grammes ammonia in his urine, together with 37·7 grammes of urea; while von Noorden reports a case which excreted 18·1 grammes urea and 1·4 grammes ammonia, the values increasing four days later to 34·2 grammes urea and 1·8 grammes ammonia, following a diet rich in protein. The urea was therefore increased twofold, and the ammonia only about one-third in this patient. At the autopsy, three weeks later, the liver was found to be markedly contracted and atrophic.

If von Schröder's perfusion experiments are recalled, and it is remembered that von Meister (11) found the urea considerably diminished after partial extirpation of the liver, then it appears that the urea formation in these patients was, as a matter of fact, only slightly affected. Hence the high ammonia values may be explained in another way than as an expression of an insufficient synthesis of urea. When ammonia is fed in the form of the carbonate or citrate of ammonium, it is apparent [Weintraud, Münzer (11)] that the patient with advanced cirrhosis has not lost his power of synthesizing urea from ammonia. The addition of considerable amounts of ammonia in the food is not followed by more than a slightly ammonia excretion in the urine. Calabrese is the only one who has obtained different results under the same conditions of experimentation.

Hence the high ammonia values of the urine in cases of cirrhosis require another interpretation. Such a conception has been furnished by Stadelmann (11). Just as an abnormal formation of acid in the system is held accountable for the high ammonia excretion in other cases, such as fevers, so Stadelmann believes this to be the cause of such excretion in cirrhosis. The system endeavours to protect itself against loss of fixed alkali by neutralizing the acids with ammonia. The fact is that von Jaksch (12) found considerable amounts of volatile fatty acids (acetic, propionic, butyric, and valerianic) in the urine of a patient with liver cirrhosis; while von Noorden and Weintraud observed sarcolactic, and Münzer, formic acid. The lowered alkalinity of the blood in cirrhosis may

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be interpreted in the same manner. An argument for the connection of the high ammonia excretion in the urine with the acidosis has been advanced by Münzer, who observed a lowering of the ammonia excretion of cirrhotic patients following the administration of sodium citrate.

The question is thus satisfactorily cleared up. The synthesis of ammonia into urea—whose chief place of formation is localized in the liver—is still maintained in cases of cirrhosis even if, according to the anatomical picture, large areas of the organ are destroyed. The breaking down of protein is carried to its normal end-products, and hence no intermediary metabolic products appear, *intra vitam*, in place of urea. It is evident that the urea-forming function of the liver is of importance to the system, in so far that perceptible disturbances of this function are not compatible with continuance of life. In cases of destruction of liver tissue by pathologic processes, the remaining glandular tissue is able to maintain for a long time the functional activity of the organ to the full extent. If the liver ceases to do this, then it is difficult to prove that a functional defect exists, because death almost immediately follows [Weintraud (12)].

The excretion of *other nitrogen-containing substances* which have their origin in the protein metabolism is differently regarded to-day than formerly.

Leucin and tyrosin, whose appearance in the urine seemed to signify a severe disturbance of the protein decomposition in the system, need not now be considered as intermediary products of the ingested protein. They are, rather, to be regarded as constituents which are washed out of the degenerating liver. Moreover, there is only one report extant of their occurrence in cirrhosis of the liver [von Greco]. Stadelmann and von Noorden have searched in vain for their presence in the urine of cirrhotic patients.

It is likewise probable that the appearance of *albumoses and peptones* in the urine is to be regarded in the same light [Hallauer (13)]. Although the liver may take an active part in the elaboration of those portions which are brought to it by the portal circulation, yet those protein derivatives which appear in the urine, are to be considered only as material washed out of a degenerating gland; and while they indicate the occurrence of a vital autolytic process, they do not necessarily signify a disturbance of the vital functions of the liver.

It amounts to this: that the clinical finding of peptonuria and of albumosuria is not free from objections in view of the methods adopted for their detection [Stadelmann (14)]. Hence, although Bouchard has found albumosuria in seventy-six patients with the most varying diseases of the liver, and Grocco, O. Brieger, and Stadelmann have failed to find it in such cases, these observations do not permit of any general interpretation (14).

It has been already mentioned that the liver in mammals and in man, as opposed to its function in birds, is not concerned in the formation of uric acid. A lowering of the uric acid excretion, by which the activity of the liver might be judged, is, therefore, not to be expected in diffuse parenchymatous disease of the liver, and, indeed, is not found in cirrhosis.

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Horbaczewski, Fawitzki, Schapiro, and Friedrichsen (15) found normal—yea, even somewhat higher values. The latter figures might depend on large nuclein content of the food, or arise from a marked formation of endogenous purin, as a result of protein decomposition. Indeed, it is not possible to make a functional disturbance of a diseased liver accountable for the increase of the uric acid excretion, although it is a function of the normal organ to convert uric acid into urea [Ascoli (15)].

Moscatelli (15) examined, with a negative result, the urine of a cirrhotic patient for allantoin, because he had found this body in the ascitic fluid.

3. Nitrogen-free Substances (Alimentary Glycosuria).

Regarding volatile fatty acids, lactic acid, etc., in cirrhosis, see p. 279. On the basis of their researches in a case of Banti's disease, and also in one of carcinoma of the liver, H. Strauss and Phillippsohn (16) assert that diseases of the liver cause an increased amount of fatty and aromatic oxy-acids and hippuric acid to be excreted in the urine.

Sugar.

The general points of view which make the appearance of sugar in the urine of hepatic patients interesting have already been discussed. This glycosuria follows as a result of a compromising influence on the glycogen-storing function of the liver, brought about by the biliary stasis. In cases of cirrhosis of the liver, besides the insufficiency of the liver cells and their alteration by the stagnation of bile, still another factor appears —namely, the altered circulation of blood.

It must be stated, in the first place, that on an ordinary diet the cirrhotic patient does not excrete sugar. Moreover, it must be especially emphasized—in opposition to the views of a few French writers [Colrat, Roger, Bouchard (17)]—that glycosuria does not belong to the clinical picture of uncomplicated cirrhosis of the liver.

When spontaneous excretion of sugar (glycosuria *ex amylo*) is observed in cases of cirrhosis [Murchison, Colrat, Couturier, Quincke], there is always a question of a combination of diabetes mellitus with disease of the liver, a coincidence which is not rare—at least, in man [Naunyn]—and which is well explained by the occurrence of a coexistent interstitial pancreatitis [F. Steinhaus]. The cases of pigmentary cirrhosis with diabetes (*diabète bronzé*) belong to this category.

From these considerations it is difficult to separate the question how cirrhotic patients who are not diabetic at the same time react to an overloading of the blood with carbohydrates. Many authors claim to have seen alimentary glycosuria in cases of cirrhosis following small doses of glucose, and this, too, in a more marked degree than in healthy subjects. The key to these assumptions lies in the older experimental observations.

Claude Bernard observed that dogs whose portal vein was gradually obliterated excreted a saccharine urine on a diet rich in carbohydrates. The blood of the intestinal veins passed in these cases through collateral circulation to the vena cava without going to the liver, which therefore

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lost its opportunity of storing up its sugar as glycogen [Heidenhain]. To this corresponds the fact that sugar was excreted in the urine much more easily after injection into a crural vein than if the same amount was introduced into a mesenteric vein, because the liver in the former case did not accumulate the carbohydrate, and, as a result, the sugar passed to the kidney, and appeared in the urine (18).

Colrat and Couturier supposed that analogous conditions obtained in men who suffered with ordinary cirrhosis, and in whom the development of a collateral circulation pointed to an obstruction of the portal vein. The result of their research corresponded to their expectation, and confirmed the brilliant experiment of Claude Bernard. In a few such cases of cirrhosis of the liver the administration of larger doses of carbohydrates resulted in a transitory excretion of sugar.

Andral, Gintrac, Frerichs, and others had previously reported an excretion of sugar in cases of thrombosis of the portal vein. Now began a series of investigations on alimentary glycosuria, which continued up to recent times, and which related merely to diseases of the liver, without reference to an existing disturbance in the portal circulation. Lépine, in repeating Colrat's investigations (in French literature the testing of alimentary glycosuria is generally called *épreuve de Colrat*), supposed that not only disturbances of the portal circulation, but also any alteration of the liver cells, may be the cause of a glycosuria, owing to an insufficient retention of sugar in the liver. He, however, obtained positive results only in cases of atrophic cirrhosis, and not in carcinoma of the liver or fatty liver.

The results which others obtained after him (18) may be best observed in the following table:

	Date.	*Atrophic Cirrhosis.*		*Hypertrophic Cirrhosis.*	
		Positive.	Negative.	Positive.	Negative.
Lépine	1876	3	—	—	—
Couturier	1876	2	—	—	—
Robineaud	1878	2	—	—	3
Valmont	1879	2	4	—	2
Hardy	1879	—	1	—	—
Vulpian-Reymond	1879	—	—	—	1
Roger	1887	5	2	1	2
Moscatelli	1889	—	1	—	—
Bouchard	1890	2	—	—	—
Schapiro	1891	1	—	1	—
Kraus and Ludwig	1891	3	4	—	4
Bloch	1892	—	3	—	1
Surmont	1892	2	1	—	3
Colasanti	1895	—	7	—	—
Bierens de Haan	1895	2	1	11	7
Achard-Castaigne	1898	2	—	—	—
Strauss	1898	1	10	—	6
Naunyn	1900	—	8	—	—
Bruining (dextrose)	1902	2	11	—	—
,, (saccharose)	1902	13	—	—	—

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According to this table, negative results preponderate in the more recent investigations, in which the authors were not convinced of the presence of sugar by the mere positive results of the reduction test. So much more, therefore, do the positive findings of Kraus and Ludwig, Bierens de Haan, and Bruining merit our consideration.

The difference in the technique of the experiments (amount, kind, and purity of the sugar used, time of administration, whether given on a fasting or a full stomach, whether in one or several doses) may partly explain the variations in the experimental results. Partly, however, these variations are traceable to the different reactions of the individual patients.

It is certain that there are cases of even far-advanced cirrhosis of the liver in which alimentary glycosuria is not more easily obtainable than in healthy subjects. In other cases, both of atrophic and of hypertrophic cirrhosis, 100 to 150 grammes of sugar (in the cases of Bierens de Haan, of cane-sugar), suffice to cause an undoubted excretion of glucose in the urine, while healthy persons do not react to such amounts with glycosuria. The clinical form of cirrhosis (whether with atrophy or with hypertrophy, whether with or without jaundice) does not seem, according to the foregoing observations, to be of decisive importance. Therefore it still remains to be determined in a larger number of cases whether this phenomenon is somewhat frequent, or, which is more probable, whether it is rare. The following points are worthy of attention :

1. Positive findings must be confirmed by certain tests for sugar, such as the fermentation test and the preparation of phenylglucosazone.

2. The possibility of a spontaneous glycosuria (light form of diabetes mellitus) must be determined by previous observations.

3. Pancreas disease or other complications should be excluded by the autopsy findings.

So long as these demands are but partially satisfied, alimentary glycosuria need not be included in the clinical picture of cirrhosis of the liver.

Regarding alimentary lævulosuria, see p. 254.

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III.—INFLUENCE OF ACUTE YELLOW ATROPHY OF THE LIVER ON THE METABOLISM.

The following discussion of the disturbances of the metabolism refers to the conditions present in the fully-developed disease.[1] Many observations of cases of phosphorus poisoning are supplementarily included, since both diseases show in common an extensive acute degeneration of the hepatic parenchyma. As a result of this characteristic, certain similar changes of the metabolism arise.

A.—INFLUENCE ON THE GENERAL METABOLISM.

An exact analysis of the general metabolism, with reference to the estimation of the energy arising from oxidation, has not yet been suffi-

[1] For literature of the pathogenesis and morbid anatomy of acute yellow atrophy, see No. 1.

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ciently carried out in cases of acute yellow atrophy. The ordinary course of a normal or subnormal temperature furnishes very uncertain evidence that the oxidation processes do not exceed the values in health. Likewise the marked diminution of all nervous influences permits the assumption that the stimuli which the tissue cells receive from the nervous system are smaller rather than greater.

In cases of phosphorus-poisoning a lessening of the consumption of food has been experimentally determined by investigations on the exchange of gases in poisoned animals.

B.—INFLUENCE ON THE PROTEIN DECOMPOSITION.

In a severe intoxication such as this condition, *a priori*, a marked decomposition of protoplasm and consequent protein dissolution might be expected. Naturally this is not to be estimated by the nitrogen output *sub finem vitæ*, for in the period of waning life all the activities of the organism are markedly reduced, and an indeterminate part of the decomposition products always remains in the body on account of failing action of the heart and kidneys.

Here may be cited an observation of F. P. Richter (3), who found that a daily nitrogen excretion of 10, 11, and 8·3 grammes occurred on an average additional intake of 3·5 grammes nitrogen. This suggested a pathologically increased decomposition of protein.

A case of von Noorden's (3) may also be mentioned. A patient with acute yellow atrophy excreted in the catheterized specimen of night urine from May 7 to 8, 4·6 grammes nitrogen. The urine was entirely drawn off by catheter during the next twenty-four hours, and contained 10·14 grammes nitrogen. The patient died the next day. Although she had taken practically no nourishment for several days, and while in the hospital had taken only light fluid diet, yet the amount of 10·14 grammes nitrogen is much higher than would correspond to the nitrogen excretion in simple inanition uncomplicated by an intoxication.

Nevertheless, definite ideas regarding the extent of protein decomposition cannot be gained from the majority of the clinical observations on metabolism, partly because the total amount of urine was not collected, and partly because sufficient data regarding the intake of food are lacking. An experiment by Rosenstein points to an increased decomposition of protein.

A patient of Senator's with acute yellow atrophy, to whom, on account of her great aversion for food, $\frac{1}{8}$ to $\frac{1}{4}$ litre of milk was administered daily for three weeks, or some tea or oatmeal gruel, excreted in the urine 61·497 grammes nitrogen in twenty-seven days; that is, by almost complete inanition (at most, 1·5 grammes nitrogen intake), there was a daily excretion of 2·662 grammes (0·063 gramme per kilogramme of body-weight). This value, however, scarcely indicates a toxic decomposition of protein, rather corresponding to the state of inanition. In starvation the nitrogen values of the urine always markedly diminish, even in healthy subjects, and only in rare cases to a lower level than the above. Nebelthau reports the case of a hysterical woman, who during four days

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of almost complete starvation excreted 4·72 grammes nitrogen—a daily average of 1·85 grammes (0·046 gramme per kilogramme of body-weight).

The case of Senator, which, moreover, recovered, does not, therefore, point to a special increase in the decomposition of protein; Soetbeer's case gave a similar indication. On the contrary, Bonanni showed, in cases of severe jaundice, that the amount of the total urinary nitrogen was regularly higher than in cases of inanition uncomplicated by intoxication (3).

Many differences in the metabolic exchanges are explained by the varying intensity of the course of the disease and of the accompanying processes of decomposition.

C.—INFLUENCE ON THE COMPOSITION OF THE URINE.

Of greatest importance is the fact, discovered by Frerichs (4), and later elaborated by his students, L. Riess and Schultzen (4), that the urea of the urine is diminished in acute yellow atrophy. In its place appear other bodies—leucin and tyrosin—which either are not formed in the normal metabolism by the cells of the body, or, if they are formed, are immediately converted into urea.

1. Urea.

Numerous observations show that the urea may be so diminished in severe cases that it can only be detected in traces in an acid alcoholic extract of the evaporated urine. Frerichs reports a case (5) in which appreciable amounts were found on the day preceding death, and these were not exceeded on the day of death. The diminution of urea is, however, not so markedly apparent in every case at the same time. Occasionally demonstrable amounts of urea are recorded, not only in the cases of Schnitzler (5), Wirsing and Albu, but also in the fatal cases of H. Rehn and Perls, T. Rosenheim, A. Fraenkel, von Noorden, E. Münzer, F. P. Richter, Winternitz, and Laub. The same is true of acute phosphorus-poisoning. While Schultzen and Riess have regarded the marked decrease of urea excretion as typical in such cases, other writers [G. Badt, Münzer, Engelien (6)] are unable to agree in this opinion.

It is surprising that the low values found by Frerichs and Riess and Schultzen have not been since recorded. When the excreted amount of urea is actually found to be unusually low, as in the above-mentioned case of Senator and the cases of phosphorus-poisoning of Münzer, then the total nitrogen is also small in amount. This may arise from the manifested aversion to food.

From the cases cited, deficiency of hepatic functions and decreased formation of urea can only be assumed if it is clear that urea precursors represent the diminished quantity of urea. Ammonia is, according to Schmiedeberg and von Schröder's theory, pre-eminently regarded as such a substance. Therefore ammonia estimations, in cases of acute yellow atrophy and phosphorus-poisoning, are of decided value; especially is this true of the relations of ammonia to total nitrogen and to urea nitrogen.

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The figures accessible are collected in the following table :

	Acute Yellow Atrophy—Fatal Cases.						
	Urine Quantity (c.c.).	Total Nitrogen (Gm. per Cent.).	Urea Nitrogen (Gm. per Cent.).	NH_3 Nitrogen (Gm. per Cent.).	Total Nitrogen.	Urea Nitrogen.	NH_3 Nitrogen.
Rosenheim	350	0·500	0·4	0·020	100	81·1	4·7
Von Noorden (I.) ..	800	4·600	3·5	0·083	100	75·4	14·2
Von Noorden (II.) ..	1200	10·140	7·2	1·840	100	71·0	18·1
Münzer	160	0·400	0·2	—	100	52·4	37·0
Richter	630	12·238	9·6	1·198	100	79·0	9·8
Soetbeer (I.) ..	170	1·240	—	0·228	100	—	18·5
Soetbeer (II.) ..	(?)	0·938	—	0·158	100	—	16·8
Soetbeer (III.) ..	200	2·726	—	0·347	100	—	12·7

The figures speak plainly enough. Although in isolated cases [Rosenheim] the relative value of the ammonia nitrogen is normal [Frerichs (7) once stated definitely that the urine may contain only traces of ammonia], yet in all the other cases the ammonia is relatively and, where somewhat more marked decomposition of nitrogenous substances occurs, is absolutely increased. In one case of Fraenkel's the ammonia in the urine was increased five-fold.

However, even this finding of increased ammonia excretion is capable of other interpretations, and is not sufficient to prove, without further elaboration, the assumption of an interference with the urea formation in the liver.

Increased acid formation also may increase the excretion of ammonia. There is sufficient evidence to show that this process plays a part in acute yellow atrophy. In the first place, such a process is to be assumed from the appearance of sarcolactic acid in the urine, which is present in large amounts in acute yellow atrophy and in phosphorus-poisoning [Schultzen (4) and others (7)].

Fatty acids are increased in the urine of acute yellow atrophy, and other abnormal acids, such as oxymandelic acid, have been detected. Diacetic acid was found in the urine in the cases of Senator and Soetbeer.

Finally, Münzer (6), as well as Soetbeer, showed, by comparing the bases, mineral acids, and acidity of the urine, that organic acids were present. Münzer has also furnished direct proof in his investigation, which has become of decisive importance in judging of the ammonia values, that the increased ammonia excretion is dependent on the acid formation in the system. He administered 6 grammes of sodium bicarbonate per diem to a patient with acute phosphorus-poisoning, with the result that the ammonia excretion was quickly diminished. While on the preceding day 16·56 per cent. of the total nitrogen was excreted as ammonia, only 11·06 per cent. was excreted on the day of the experiment, in spite of the fact that a part of the bicarbonate was lost by vomiting ; on the next day only 6·2 per cent. was found. Hence the introduction of the fixed alkali brought about a diminution in the excretion of

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ammonia; and so the increase of ammonia can have only one meaning—namely, the neutralization of abnormal acids. The ammonia values in Soetbeer's observations, which were high in spite of a simultaneous administration of alkali, may also be explained in this way.

The pathology of metabolism, even in diseases of the liver, does not furnish conclusive proof of the validity of von Schröder's theory of urea formation from ammonia; for those cases in which there is the most extensive destruction of liver cells should yield evidence of the abolition of hepatic functions.

It is not necessary, however, to abandon a theory so well founded experimentally, although its application must be limited. The cited animal experiments demand its limitation in this way—namely, that along with the liver, which is the chief formative organ for urea, other tissues must be considered as able to bring about its synthesis. If the meaning of the liver as the urea-forming organ does not become more evident in human pathology, then this condition may, as already mentioned, depend on the fact that the hepatic function under discussion is so vital and so inseparably bound up with the existence of the organism that life becomes extinct if the formation of urea is really lessened in the first place. However, when death arises in severe diseases of the hepatic parenchyma, without a disturbance of this function becoming evident, then life must become extinct for other reasons, perhaps owing to an intoxication which affects the central nervous system or the heart. In this connection, compare the researches of H. Meyer, in which animals poisoned with phosphorus sometimes died rapidly from failure of the heart at a time when the poison had not affected any other part of the body.

2. Leucin and Tyrosin.

The explanation of the presence of leucin and tyrosin in the urine in pathological conditions accompanied by decomposition of hepatic tissue, has been rendered less difficult by the recent investigations upon autolytic processes.

As soon as Frerichs and Schultzen and Riess (4) had discovered these two acids in the urine in cases of acute yellow atrophy, and had proved that they did not arise from accidental decomposition of the urine, but were actually present in the urine as preformed bodies, then the assumption was very natural that in these cases protein cleavage products were excreted as a result of a disordered formation of urea. That leucin could be regarded as a precursor of urea the feeding experiments with glycocoll and leucin seemed to show, inasmuch as an increase in the urea excretion was observed, while no leucin appeared in the fæces. Nevertheless, Hoppe-Seyler (8) doubted that leucin and tyrosin were normal intermediary products of protein decomposition, and even if such were the case, it is still necessary to inquire whether the liver is able to split off the ammonia from the amido-acids.

Further, the question arises, Whence come these amido-acids, which up to the present time are recognised only as products of pancreatic digestion and of putrefaction of protein? They appear to arise from

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the degenerated liver, from which after death it is possible to obtain larger amounts of leucin and tyrosin than occur in the urine [Frerichs and Städeler, Röhmann, Taylor (8)].

How do these substances get into the liver? What is the stimulus in cases of acute yellow atrophy which causes the protein decomposition to take this course? Why are these intermediary products deposited in the liver? The assumption that the presence of tyrosin is due to bacterial action is not improbable if the hypothetical infectious origin of the disease is accepted. However, in cases of phosphorus-poisoning, in which bacterial action may be excluded, the view must be widened so as to ascribe the tyrosin to an absorption from the intestine.

The investigations of Jacoby, Schryver, and others on autolysis of the liver have placed the question in a new light (9). In aseptic auto-digestion, the amido-acids under discussion are formed in the liver from the cellular material of the organ—more abundantly in the livers of animals poisoned by phosphorus than in normal autolysis. This is the key to the origin of leucin and tyrosin. These amido-acids are not regularly found in acute yellow atrophy; and if they are found, at one time abundantly, at another only in traces, it is to be remembered that they appear, not only in cases of yellow atrophy and of phosphorus-poisoning, but occasionally in other diseases, such as leuchæmia, small-pox, and typhoid. The quantities vary, and the conditions determining their disappearance from the organ are different from case to case. Thus are explained the facts that Frerichs and Schultzen and Riess found in one case 1·5 grammes of tyrosin, along with abundant leucin, in the total twenty-four hours' urine, while Rehn, Perls, Röhmann, Rosenheim, A. Fraenkel, O. Brieger, von Noorden, Senator, F. P. Richter, and Albu failed to find either. Riess (7) detected them thirteen times in fourteen cases of acute yellow atrophy, but only exceptionally in cases of phosphorus-poisoning, in which condition Schultzen and Riess had originally absolutely denied the presence of these bodies on the basis of their own negative researches. The attempt to base a differential diagnosis between these diseases on the differences above stated was, however, unsuccessful.

In this way are also explained the contradictions that the excreted amounts of leucin and tyrosin are often slight—yea, that these substances may be absolutely lacking in the urine; and yet large amounts of these acids may be obtained from the liver after death [Frerichs, Röhmann]. Their origin is always traceable to the more or less extensive degenerative decomposition of the liver cells during the disease [Jacoby (9)], and their excretion in the urine is dependent on an overloading of the system with the products of this decomposition. Along with this many factors, such as solubility, relations of circulation and absorption, may each play a part, so that the results may be somewhat different.

Likewise the appearance of a large number of organic acids (lactic, acetic, butyric, and succinic acids) in the urine of patients with acute yellow atrophy has become intelligible through the investigations on autolysis of the liver [Magnus-Levy 9)].

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3. Peptone and Albumoses.

The conception of peptonuria has suffered many changes [Stadelmann (10)], and the ideas prevalent during the earlier decades regarding the excretion of peptone and albumoses in the urine are not to be accepted without further investigation.

Schultzen and Riess (4) report the finding of peptone-like bodies in the urine in cases of true acute yellow atrophy of the liver, and especially in cases of degeneration of the liver following phosphorus-poisoning. It is not possible to-day to determine with what bodies these writers were working at that time, for the identification of peptone in their analyses left much to be desired. In all of the later data regarding the albumose content of the urine in cases of acute yellow atrophy there is a question of only small amounts, just as is the case in many other diseases. Thus, Thomson and von Noorden report positive findings and O. Brieger negative results in acute yellow atrophy; while in phosphorus-poisoning Maixner obtained positive results, von Jaksch twice positive and once negative, Badt and von Noorden once doubtful and once negative, Münzer five times negative, and Senator negative (10). It is certain that these substances do not play a part in the partition of nitrogen in the urine. It is always possible to derive albumoses from the decomposing hepatic tissue, which after death contains these substances in large amounts [Salkowski, Röhmann, Miura (11)]. According to the investigations of Hallauer (11), there is no longer any doubt as to this origin of the albumoses.

4. Purin Bodies.

Although Röhmann (8) obtained 8·6 milligrammes (more than twice the normal amount) of xanthin silver from 100 c.c. of urine in a case of acute yellow atrophy, yet, reasoning from our present knowledge of purin metabolism, the cause cannot be considered as only due to an increased formation of endogenous purin. The source of the endogenous purin is the nuclear decomposition in the degenerating tissues. Hence the liver contains purin bases in abundance.

In the mammalian organism the function of uric acid formation is not ascribed to the liver. The few uric acid estimations which have been made in cases of acute yellow atrophy likewise point to this fact. Von Noorden (12) found in the night urine (800 c.c.) 0·432 gramme, and in the total twenty-four hours prior to death 0·36 gramme of uric acid. In relation to total nitrogen, there was a relatively high percentage (3·1 per cent.) in the first urine, while in the second there was a much smaller percentage (1·2 per cent.).

In a case of true acute yellow atrophy it was possible, ten days before the death of the markedly icteric patient, to increase the excretion of uric acid almost 1 gramme by feeding with calves' thymus, as the following table shows [Weintraud (12)].

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No.	Urine—		Total Nitrogen.	Purin Base Nitrogen.	Uric Acid Nitrogen.	P_2O_5.	Remarks.
	Quantity.	Specific Gravity.					
	C.c.		Gm.	Gm.	Gm.	Gm.	
1	1,140	1009	4·40	0·249	0·442	0·410	—
2	2,360	1008	5·55	0·314	0·485	1·369	—
3	4,100	1010	15·09	0·687	1·402	2·993	Thymus.
4	2,800	1010	7·09	0·492	1·056	2·296	—
5	1,800	1010	5·62	0·369	0·824	1·746	—
6	1,800	1009	6·04	0·322	0·801	1·296	—
7	1,200	1010	5·07	0·317	0·364	1·344	—

The high uric acid values which Badt (6) found in a case of phosphorus-poisoning correspond to the increased production of endogenous purin as a result of degeneration of tissue in cases in which the formation of uric acid is not disturbed. In a patient which died on the eleventh day he found 1·818 and 1·446 grammes on the ninth and tenth days of the disease. In a second case the excretion was only a few centigrammes. Münzer (6) likewise reported quite appreciable amounts.

Boese (13) has obtained *inosinic acid* in traces in the urine of acute yellow atrophy.

Nitrogen-free Substances.

Lactic acid has already been discussed. It is found in acute yellow atrophy, as well as in phosphorus-poisoning. It cannot, however, be accepted as proven that in the latter condition lactic acid is found more abundantly, as Schultzen and Riess maintain.

Lépine (13) reported an increased excretion of the non-oxidized phosphorus in the urine in a patient with fatty degeneration of the liver. Its appearance must be traceable to the increased lecithin content of the fatty liver.

5. Aromatic Oxy-acids.

Schultzen and Riess and Röhmann (8) prepared oxymandelic acid from the urine of a case of acute yellow atrophy; its presence is not restricted to acute yellow atrophy. Baumann has reported data regarding oxymandelic acid in two cases of phosphorus-poisoning, and van Ackeren in one case. Blendemann once found in phosphorus-poisoning 0·2475 gramme of a non-identified aromatic acid (14).

The aromatic acids are derivatives of tyrosin, and hence appear in traces in healthy urine also. However, in the autolysis of the liver they have not as yet been detected. In several of the reported cases these acids appeared in appreciable amounts, while tyrosin was not found in the urine. This is clearly evidenced by Röhmann's observations. According to him, the diseased tissues are, under certain conditions, still in a position to split off the ammonia radical from tyrosin, and to inaugurate the oxidation of the aromatic nucleus, but are no longer in a position to bring this oxidation to completion. In such cases only aromatic oxy-acids would be excreted, but no tyrosin. Recent work suggests that also in autolysis the aromatic oxy-acids may be formed.

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6. Sugar.

Sugar has been found in the urine of acute yellow atrophy only by Tscherinoff and Soetbeer. In phosphorus-poisoning it is also rarely found, Bollinger and Huber recording the presence of traces, and Reichel observed 1·3 per cent. of sugar on the third day of the poisoning. Laub found 0·67 per cent. on the fourth day, and 0·15 per cent. on the eleventh day, while in a second case he observed 0·45 to 0·69 per cent. nine days after the poisoning. In his first case an alimentary glycosuria, following the administration of 100 grammes of glucose, was noted on the twenty-second day of the disease. Von Jaksch concludes from his observations that glucose introduced in excess is no longer completely oxidized—at least, in certain stages of the disease (15).

7. Biliary Constituents.

The urine, in cases of acute yellow atrophy, usually contains a large amount of bilirubin, and that, too, up to the time of death. From this fact it must be concluded that the formation of biliary pigment remains constant in spite of the severe injury to the hepatic parenchyma.

The passage of biliary pigment into the blood in cases of yellow atrophy arises from the biliary stasis, partly as a result of the swollen condition of the liver cells, by which the smaller bile-ducts are compressed, and partly as a result of the abnormally tenacious property of the bile. If it is to be admitted at all, then it may be conceded that a secretion anomaly of the liver cells is present in these cases (paracholia, parapedesis). Only in a few cases is the biliary stagnation so complete that the fæces are completely decolorized. Although large amounts of green bile are frequently vomited, yet appreciable portions of the abundantly-produced pigment still pass into the intestine, so that large amounts of hydrobilirubin may be formed, which are absorbed and excreted in the urine [Wirsing (1)]. The possibility of urobilin formation in the degenerating liver has already been discussed.

In acute yellow atrophy, therefore, a marked dissolution of red blood-corpuscles must occur either in the blood current itself, or in the tissues, following a true hæmorrhage. This has also been accepted for phosphorus-poisoning since the experimental investigations of Fraenkel and Röhmann (16). The blood changes are discussed later.

Biliary acids have been definitely demonstrated in the urine of acute yellow atrophy [Hoppe-Seyler, Thierfelder (17), Soetbeer (3)], but they are often present only in traces, and in some cases are entirely absent [Rosenheim, Wirsing].

D.—INFLUENCE ON THE BLOOD.

Little is known of the composition of the blood in acute yellow atrophy. The increased production of biliary pigments points, as has been already mentioned, to an accelerated dissolution of red blood-corpuscles. The only available blood count [E. Grawitz (18)] showed 5,150,000 erythrocytes. In phosphorus-poisoning also the number of red blood-corpuscles is high. Thus, Taussig (18) reported a considerable

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increase in part of his cases, while von Jaksch (18) observed an increase, and von Noorden counted 6,700,000 to 6,800,000 during the height of the disease.

These figures have led Münzer to the conclusion that no further dissolution of blood-corpuscles takes place in phosphorus-poisoning. Taussig even assumed an actual transitory increase in the number of erythrocytes. The high counts of the red blood-corpuscles do not show in themselves any absolute increase of erythrocytes in the total volume of blood. There might be a question here of an apparent (relative) increase, which might arise in the following way: the loss of the water or plasma from the blood might momentarily be greater than the dissolution of the corpuscles as a result of influences causing an increased lymph-flow or of vasomotor disturbances [von Noorden, E. Grawitz]. The values found by E. Grawitz in the case of acute yellow atrophy already mentioned certainly give no basis for this assumption. He found 20·7 per cent. of solids of the blood, and 7·77 per cent. of the serum. Likewise von Jaksch found the protein content, as well as the water content, of the total blood and blood-serum to be quite normal.

Morphologically, the red blood-corpuscles in phosphorus-poisoning do not appear to be much changed [von Jaksch], yet the phenomena, already mentioned as occurring in jaundice, of disordered formation of rouleaux and of premature thorn-apple formation has been frequently reported in acute yellow atrophy and phosphorus-poisoning [von Noorden, Grawitz, von Jez (19)].

In similar manner, the decrease of the alkalinity of the blood [F. Kraus and von Jaksch] speaks with certainty for an increased cellular decomposition in the blood [Münzer (19)]. On the other hand, this condition may be traceable to the absorption of certain protein decomposition products, which are formed by the influence of intracellular proteolytic ferments in pathological conditions. Yet Neuberg and Richter were able to obtain from the blood of a patient with acute yellow atrophy such large amounts of leucin, tyrosin, and lysin, that the exclusive origin of these amido-acids from the protein constituents of the liver cannot be longer accepted.

Winterberg (20) was unable to determine an increase in the ammonia content of the blood.

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IV.—DISTURBANCES OF THE ANTITOXIC FUNCTION IN DISEASES OF THE LIVER.

Many years ago it was considered that the liver retained poisonous substances which reached it from the intestine, and thus protected other cells of the system from contact with these poisons. Such an assumption was based on the anatomical position of the liver, and on the special arrangement of its blood-supply. It has received an essential support in the experimental proof of the particular relations which the liver shows to certain exogenous poisons (alkaloids and metals).

When Schiff ligatured the portal vein, and attributed the death of the animal to the action of metabolic poisons normally retained or detoxicated by the liver cells, Héger was able to show by artificial perfusion experiments that the liver held back 20 to 25 per cent. of poisons added to the blood, such as nicotine, hyoscine, strychnine, morphine, and quinine.

Further animal experimentation furnished the corroboratory evidence that alkaloids injected into the veins of the ear show much more marked phenomena of poisoning than when they are injected into the portal vein [Schiff, Lautenbach, Lussana, Jaques]. In attempting to explain these facts, the opinions of the writers were in the first place divided as regards the question whether the liver retains and stores the introduced poison in an unchanged condition [P. Héger, Jaques], or whether it unites chemically with these substances, and converts them into less poisonous or harmless substances [Schiff, Lautenbach], or, thanks to its eliminatory power, excretes them in the bile [Lussana (1)].

All of the earlier experiments were later repeated and extensively elaborated by Roger (2), under the direction of Bouchard. Roger, in his voluminous monograph, comes to the following conclusions: The liver does not render potassium and sodium salts harmless. It stores up certain mineral poisons, such as copper, arsenic, antimony, and mercury. It acts energetically upon certain salts of iron, so that lactate of iron, for instance, is three times more poisonous when injected into the veins of the ear than when introduced into the portal vein.

Plant alkaloids and putrefactive ptomaines lose, without exception, one-half, and often more, of their poisonous properties if they pass through the liver before their entrance into the general circulation. The same thing is true of the decomposition products of protein (peptone and ammonium salts), and of the still unknown organic poisons which are found in normal urine.

This detoxication is not due to the excretion of the poisonous substances in the bile, for bile contains only traces of alkaloids. It is, moreover, not dependent on simple storing up of the toxic substance. The liver forms new less poisonous compounds from the toxic substances by accumulation of carbohydrates. For this end the presence of

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glycogen in the liver is an essential factor. If the liver is made glycogen-free by hunger or experimental methods, then it loses its disintoxicating power, and, *vice versa*, all of the substances introduced produce a less toxic action if the glycogen content of the liver is increased by simultaneous administration of glucose [Roger].

The advocacy of this alleged parallelism of two hepatic functions —namely, of the glycogenic and the disintoxicating functions—has in France become the point of departure for the further elaboration of the question of disturbed hepatic function. The formulation of the present theory of hepatic insufficiency has now replaced the above idea.

Roger himself tested the validity of his assumption in the clinical part of his work. Since mere superficial disturbances of the liver, such as simple stagnation of bile, lessen the supply of glycogen in the liver, then it is to be expected that in diseases of the liver the poisons produced in the body, and especially those arising from the intestine, overload the general circulation, and are excreted in the urine. Roger examined the urine of a patient with liver disease, with reference to its toxicity on rabbits, according to Bouchard's method. He found the toxicity coefficient many times greater than normal in several cases of catarrhal jaundice, cholelithiasis with biliary stasis, atrophic and hypertrophic cirrhosis. In other cases the increase in the urinary toxicity was lacking.

In view of these diverse relationships, it seemed advisable to investigate whether large doses of sugar would produce glycosuria in the respective patients. It was shown that very toxic urines were likewise saccharine. Roger united these two findings in his explanation that the liver was not able to store up glycogen, and therefore could not render the poison harmless. In the other cases the liver still has the power of accumulating glycogen, and hence maintains its disintoxicating power. No attempt was made to isolate the toxic bodies from the urine, but Roger concludes that the biliary pigment among them plays an essential rôle.

Following Roger's work, a number of investigations were made upon the retention of poisons in the liver, and a protective action of that organ was assumed. Thus, Capitan and E. Gley investigated antipyrin; Gley and Eon du Val, cocaine; Roger, strychnine; A. Schmidt, morphine-esters; Schupfer, various alkaloids; Legry, Charrin, and Brunton, bacterial poisons [Pestana (3)].

On the other hand, René (4), whose research Roger has, it is true, severely criticised, disputes the protective action of the liver as regards nicotine. Chouppe and Pinet (4) regard the observed reduction in the action of strychnine as only a result of retarded absorption of the poison. Sauer opposes the idea of a conservative action of the liver as regards curare, which action Lussana, Albanese, and Gaglio (4) claim to have demonstrated.

Kotliar (5), by an ingenious method of research, has set aside all doubts of the antitoxic function of the liver. In one experiment he ligatured the portal vein of dogs with Eck's fistulæ (communication between the portal vein and the inferior vena cava), so that the portal blood reached the general circulation without passing through the liver, and observed that administration of atropin *per os* called forth the same severe pheno-

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mena of intoxication, both as regards the cardiac and the pupillary reactions, as if the drug were given subcutaneously. In another experiment with animals prepared in the same way he ligatured the inferior vena cava, and thus caused the entire venous blood of the lower half of the body to pass through the liver. He showed that, under these circumstances, the poison injected into the femoral vein exerted a much weaker action than in the control animals, or than was observed after injection into the veins of the head.

The chemical processes bringing about the antitoxic action of the liver cells have become more intelligible as a result of the investigations which are concerned with the retention in the liver of inorganic poisons—namely, of the heavy metals. It has been known for a long time that, by injection of iron salts into animals, large amounts of these were retained by the liver, with the formation, not only of iron-containing proteids, such as ferratin, but also of iron-containing nucleo-proteides of the liver. It is now more than probable that iodine combines with a definite globulin in the thyroid [F. Blum, A. Oswald (5)]; likewise it must be granted that arsenic is bound chiefly to the nucleins of the tissues and leucocytes. Slowtzoff has also shown that mercury enters into combination with globulin in the liver, while arsenic and copper unite with the nucleins of the liver (5).

Slowtzoff brings the fact that animals under forced feeding are better protected against poisoning than are starving ones into relationship with the fact that the forced feeding increases the supply of protein just as much as it does that of glycogen. By reason of this higher protein content the liver has a greater power of combining with poisons. Hence one should generally assume that it is not simply the glycogen content of the liver which makes it capable of combining with poisons, but it is rather the total protoplasmic material of the liver.

In this sense, the recent investigations of Vamossy (5) regarding the accumulation in the liver of copper, mercury, arsenic, zinc, lead, strychnine, atropine, and quinine are likewise interpreted.

Buys assumed, on the other hand, that we have to do with a question of the action of an antitoxic principle which is dissolved in the tissue juice of the liver, inasmuch as he observed in his experiments that hyoscyamine, when added to freshly-prepared liver pulp, completely lost its action on the pupil. Likewise, Petrone and Amendola noted *in vitro* an antitoxic action of the liver on plant alkaloids.

On account of the doubtful value of the methods used, we may omit from discussion the work which has been concerned with the urotoxic coefficient of the urine of hepatic patients (7).

The toxicity of the urine in cases of severe hepatic disease is increased, because the poisons which arise during digestion and putrefaction in the intestines, and which would normally be rendered harmless by the liver, are excreted in the urine. Exception may, however, be observed if periods of lessened functional activity of the kidneys arise in the course of the hepatic disease. In such cases the poisons are retained in the system, and may in cases of infectious jaundice (Weil's disease), show a critical excretion after the crisis [*crise urinaire des hépatiques*, Chauffard

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(8)]. On account of the danger of auto-intoxication, a high toxicity coefficient of the urine is a favourable prognostic sign, while a low urinary toxicity is an unfavourable omen.

In the same way, H. Schapiro employed for purposes of prognosis the excretion of strychnine administered in small doses. This was found to be excreted in the urine much quicker if the liver was diseased and did not possess the power of retaining the poison.

Excretion of metabolic poisons occurs, not only in the urine, but also in the bile. The toxicity of the bile decreases after ligature of the portal vein, as a result of diminished supply of poisons from the intestines to the liver [Lugli (9)]. Hence, in cases in which the permeability of the kidney epithelium is sufficient, the poisons pass into the urine, whose toxicity is therefore increased after ligature of the portal vein [Bisso (9)].

Some investigations, however, do not support the view of a protective action of the liver against the poisons brought to it by the portal blood. Indeed, after the liver has been rendered inactive by means of Eck's venous fistula, dogs exhibit the symptoms of a severe intoxication when they are given protein food [M. Hahn, V. Massen, M. Nencki, and J. Pawlow (10)]. Animals whose portal blood is conducted through a cannula into the inferior vena cava excrete a urine which, tested by Bouchard's method, is not more poisonous than that of sound animals [Queirolo (10)]. Just as little do peritoneal transudates (ascitic fluid of hepatic cirrhosis) show a greater toxicity than pleural exudates after intravascular injection of the poison. This fact suggests that the blood circulating in the branches of the portal vein possesses no greater toxicity than that found in the general circulation [Queirolo].

Although the experiments of Bouchard are very suggestive, one must, nevertheless, not conceal the fact that they furnish only a very superficial perspective regarding the various poisons of the system and the relations of the liver to them. Judging from the adverse criticism to which Bouchard's method has been generally subjected, it is improbable that our knowledge will be extended by continuing such research. It is much more profitable to determine the exact nature of those bodies which make the urine of hepatic patients so toxic, so that their source may be determined with greater certainty. The further elaboration of qualitative urinary analysis, and especially the continuation of the efforts to ascertain the chemical nature of the residuary nitrogen of the urine, will be the first and most effective method of solving this problem.

Further, it should be shown experimentally what share is assigned to the liver in converting the poisonous products of digestion or of cell activity in the system into less poisonous compounds by reason of its power of retaining these poisons. Regarding the aromatic cleavage products of protein which arise during intestinal putrefaction, Baumann has expressed the view that their conjugation with sulphuric acid takes place in the liver, inasmuch as more conjugated sulphuric acid occurs in the liver than in the other organs (11). On the basis of perfusion experiments on the extirpated liver, Embden and Glaessner have recently shown that the liver is likewise the place of the conjugation with the ethereal sulphuric acids (11). It appears probable that the formation

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of conjugated glycuronates, which may possibly mean a neutralization of the toxic substances, takes place partly in the liver (11). According to the investigations of Fr. Pick, the liver is less concerned in this latter function than are other organs (11). A discontinuance of this synthesis has, moreover, not yet been observed in hepatic diseases.

Whether the liver exerts an antitoxic action against the diamines by utilizing them for the synthesis of cystin has again become very questionable. No excretion of cystin is observed—at least, in dogs—on feeding with diamines [Baumann and Udranszky (12)]. On the other hand, according to the experimental evidence of animal investigations, the liver appears to play a specific rôle in the formation of taurin from cystin [Bergmann, A. Blum (13)]. To this same idea points an observation from human pathology. In a patient with cystinuria, who was suffering at the same time with atrophy of the liver, Marowsky (13) observed a constant, almost complete, acholia of the fæces. He considered that cystin was vicariously excreted for taurin as a result of a disturbed hepatic function. An increase of cystin in the urine has been observed by Baumann and Goldmann (13) in a case of phosphorus-poisoning.

The relation of the utilization of the sulphur-containing cleavage products of protein in the formation of bile to the disintoxication processes is too little determined to permit us to multiply such observations in this place, or to further elaborate them.

Finally, the formation of bile is a specific vital function of the liver, and it is self-evident that its involvement or abolition as a result of pathologic changes in the organ cannot continue without severe reactions upon the system in the sense of an auto-intoxication. The same thing is true of the antitoxic function of the liver as regards ammonia, although the urea formation is not localized in the liver to the same exclusive extent as the formation of bile (14).

The antitoxic functions of the liver may be, to a great extent, comprehended by recognising a protective action in each of the numerous metabolic indications by which the functional activity of the normal liver cell manifests itself, and by seeing an intoxication in the disturbances of these functions. At all events, the normal composition of the tissue juices is altered, and they depend upon hepatic integrity for their adequate maintenance.

Just as the synthesis of urea from the toxic ammonia permits the harmless urea to be excreted, so the formation of glycogen from the carbohydrates prevents an overloading of the system with glucose. The poisonous products of the digestion of protein (peptones) are converted, during their passage through the liver, into non-toxic compounds, while the free fatty acids and soaps which arise in the intestinal digestion of fats, and which are toxic in large amounts, are retained and stored up in the liver. The formation of bile likewise frees the body from other injurious products of cell activity.

Without considering these functions of the liver from the teleologic standpoint, German works have busied themselves with the analysis of single phases, and endeavoured to become acquainted with their normal and pathological course.

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On the other hand, in France the theory of hepatic insufficiency, which has been constantly elaborated during the last two decades, is concerned with the point of view of the reaction of the functional activity of the liver as a whole upon the system of the healthy and of the diseased person.

In spite of much ingenious elucidation which certain sections of pathology have received from this standpoint, yet it signifies, as a matter of fact, scarcely more than an enrichment of our nomenclature. Thus, one speaks of hypohepatia or anhepatia if the function of the liver appear to be involved or abolished, and of hyperpatias, both anatomical and functional, if hyperbiligenesis, hypercholia, hyperazoturia, hyperglycæmia, etc., point to an increased activity of the liver. Similarly, as little value has resulted from the combination of a number of findings, such as urobilinuria, alimentary glycosuria, hypoazoturia, increased excretion of ammonia, indicanuria, etc., in the symptom-complex of incomplete hepatic insufficiency (*syndrome du petit hépatisme*), or from the designation of the cholæmic phenomena of severe jaundice as the symptom-complex of complete hepatic insufficiency (*syndrome du grand hépatisme*).

It is possible that we should accept for the phenomena of hepatogenous intoxication in cases of complete hepatic insufficiency a more suitable expression than the ambiguous term "cholæmia." The designation of "acholia," which Frerichs (16) selected for this condition, is no more suitable. It may be that the term "hepatargia" (*ἀργία* = inefficiency), advocated by Quincke (16), may arise in its place.

In general, there is too little constancy in the so-called hepatic insufficiency to warrant the assumption of a clinical symptom-complex corresponding to it. Moreover, the diagnostic signs so frequently enumerated in French literature are likewise of little avail in the recognition of liver insufficiency.

The hydrogen sulphide test (appearance of an odour of hydrogen sulphide in the expired air after the use of enemata of hydrogen sulphide-containing water) is very uncertain [Roger and Garnier (15)]. The intermittent and cyclic excretion of methylene blue, which Chauffard (17) regards as characteristic of hepatopathies, is in no way peculiar to diseases of the liver. Still less is this the case with indicanuria, which Peaudeleu (17) claims as a sign of a hypohepatia. Regarding the inconstancy of alimentary glycosuria, whose meaning is still very much overrated in this regard, see p. 283 [Roger (2), Linossier (17)]. The proposal of Kolisch to recognise an indication of hepatic insufficiency in the increased ammonia excretion which follows the overloading of the liver with large amounts of nitrogenous material (50 grammes of nutrose) has found no general application. Likewise the idea of E. Schwarz, that the excretion of administered lactic acid should be regarded in the sense of a hepatic insufficiency, has not proven itself to be practical.

Just so the investigations, conducted with a view of obtaining a test of the functional activity of the liver by administration of sodium butyrate and by estimation of the volatile fatty acids excreted in the urine, have not proven very satisfactory, because the increase of fatty acids

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is not sufficiently constant (18). The so-called alimentary lævulosuria, which was first advocated by Strauss as characteristic of disordered hepatic function, has alone received general recognition through numerous confirmations.

It is difficult to say just how far other organs are functionally or anatomically altered by the toxic action which arises as a result of the disturbances in the liver. The French literature uses, to a great extent, the expression hepatotoxia for these changes [Chauffard (19)].

It is true, however, that in many cases several organs, separately and simultaneously, may be primarily affected by the etiologic factor of the disease. Thus, for instance, in Weil's disease the phenomena of kidney disturbance are co-ordinated with those of the hepatic disease. A certain dependence of conditions is often present. Gouget (19) has studied, in an extensive piece of work, the influence of hepatic diseases upon the kidney. Hürthle has observed an anatomically controllable influence of jaundice upon the thyroid gland in dogs after ligature of the ductus choledochus. He likewise noted this influence in cases of toluylendiamine-poisoning, a finding which W. Lindemann (19) conconfirmed in four cases of chronic jaundice.

For a hepatotoxic genesis of diseases of the nervous system (apart from the symptoms of cholæmia [Leopold-Levi]) there exist numerous clinical observations (neuritis, C. Gerhardt, Kausch; psychopathies, Charrin and Joffroy [20]). The question of the nature of the active poisons in such cases does not here call for consideration.

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CHAPTER VI

DISEASES OF THE RESPIRATORY AND CIRCULATORY ORGANS

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Diseases of the organs of respiration and circulation have this in common: that they impede the act of respiration and the supplying of the tissues with O_2. They affect the metabolism each in the same manner, although, as will be shown later in detail, they work in different ways. The supply of O_2 to the tissues is also impaired in the anæmias, or in atmospheres at reduced pressure; in the former case because the oxygen-carriers are fewer, in the latter because the partial pressure due to the O_2 is diminished (see Literature). Yet other changes in the metabolism of cardiac and pulmonary disease are caused by infective processes; most of these are discussed in the section on fever. Finally, each particular disease of the heart or of the lungs may give rise to changes in the metabolism peculiar to itself.

The impairment of the supply of O_2, which is common to all these conditions, may first be considered. The body is able to compensate this deficiency in a variety of ways. Respiration can be both quickened and deepened, producing the state commonly known as dyspnœa. In dyspnœa there is a subjective feeling of air-hunger, with a visible acceleration and strengthening of the respiratory movements. This condition is observed before any actual impoverishment of the blood in oxygen can have taken place, as Kraus has clearly pointed out. Further compensation can be obtained by increasing the speed of the blood stream; perhaps also by changes in the glandular functions of the lungs, or in the activity of the hæmoglobin that carries the oxygen. Each of these methods must be carefully examined before the vital processes occurring when the supply of oxygen is impaired can be clearly understood. This is all the more necessary because some of these methods, particularly those involving muscular exertion, have no compensatory action, but even increase the consumption of and the demand for oxygen.

In the second place, the changes that take place in the metabolism when these methods of compensation are no longer adequate must be discussed. The question whether such a condition of affairs is compatible with life arises naturally in this connection. It might be supposed that the tissues would generally limit their consumption of O_2, and that the intensity of the metabolism would be diminished; or else it might be assumed that a qualitative change would occur in the meta-

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bolism, the processes of oxidation and combustion not proceeding as far as to the development of the normal end-products. In either case the production of heat would be diminished, and this diminution might more than balance the increase due to the augmented (compensatory) activity of the heart and the respiratory muscles.

Hence it is necessary to outline the methods and extent of the compensation provided, and to find out whether the changes in the compensation are quantitative or qualitative.

A.—PHYSIOLOGICAL CONSIDERATIONS.

It is well known that under normal circumstances the oxyhæmoglobin in the blood is not fully reduced, and that the venous blood still contains a considerable amount of oxygen. According to the most recent researches of Loewy (1), human venous blood is 67·6 per cent. saturated with O_2, so that much more oxygen is supplied to the tissues than they consume. It should be noted that this is the normal state of affairs; the tissues are bathed in oxygen, to quote Krehl, and any variation from this condition is pathological.

Pflüger's well-known experiments show that the demand of the tissues for oxygen is quite independent of its supply. The metabolism is not regulated by the supply of oxygen, but by the demand for oxygen made by the cells. Stich found that this rule holds good for plants, as it does for animals. Should the supply of oxygen be insufficient, or even cut off altogether, the processes of combustion do not cease—at any rate, in cold-blooded animals. Thus the frog continues to evolve CO_2 in an atmosphere free from O_2. The metabolism of anaerobes sufficiently shows that both life and function can survive the deprivation of oxygen. CO_2 is produced, and oxygen for its formation is split off by the organism from readily reducible substances, and is devoted to the oxidation of other substances possessing a greater affinity for it. Oxygen so obtained is described as "intramolecular."

Pflüger's doctrine that the consumption of oxygen is ruled by the needs of the cells held undisputed sway for ten years. Recently, however, it has been attacked by Rosenthal (3), whose experiments upon warm-blooded animals have proved that more oxygen is taken up from an atmosphere rich in O_2 than corresponds to the simultaneous consumption of oxygen. Rosenthal believes that the tissues have the power of accumulating oxygen in the shape of some compound whose formation is associated with the liberation of only a small amount of heat, and that the protoplasm can break down this compound later, with the formation of H_2O, CO_2, etc. "The quantity of this intracellular oxygen is variable," writes Rosenthal; "if the supply of O_2 is deficient, the formation of the end-products at the expense of the intracellular oxygen can go on so long as the supply of it holds out." Verworn (4) and his pupils have been led to similar conclusions, although they made no direct measurements of the oxygen in question. Verworn considers that, to some extent, the nervous tissue has the power of storing up oxygen in certain

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places which he calls oxygen depots. In cold-blooded animals the degree to which this storage occurs depends mainly upon the temperature; more oxygen is accumulated at low than at high temperature. It is expressly stated (see Bondy) that the amount of oxygen in one of these depots depends upon the partial pressure of the O_2 in the fluid that bathes and nourishes it. If this partial pressure falls, O_2 diffuses out of the depot, even during narcosis.

So far Rosenthal's results have not been confirmed; in fact, other investigators contradict them most emphatically. Falloise (5), for example, finds that if an animal is previously given pure O_2 to breathe, asphyxia occurs forty-five seconds later than it does under normal conditions; this increased resistance to asphyxia is, however, lost if the animal is given atmospheric air to breathe for one minute after it has had the O_2. Falloise concludes that no storage such as Rosenthal suggests can take place, but that a physical absorption of more O_2 occurs in correspondence with its increased partial pressure. Durig (6) came to the same conclusion experimenting with dogs in a modified Geppert-Zuntz apparatus. He found that only a transient oversaturation of the blood with O_2 took place under increased O_2 pressure; the excess of O_2 was promptly given up when the O_2 pressure fell. All the older investigations stand in contradiction to Rosenthal's results—the experiments upon caisson disease may be mentioned in particular. Hence the law enunciated by Pflüger may still be accepted as correct.

Before considering in detail the provisions made for compensation, this section may be closed by a few words upon the share taken by the heart and the muscles of respiration in the normal metabolism. Zuntz calculated that 5 per cent. of the O_2 taken in by persons at rest was used up by the heart, while 10 per cent. was consumed by the respiratory movements. These values are considerably raised when larger claims are made upon the activity of the heart and lungs, and their consumption of oxygen is above the normal when they are called upon to compensate for disease.

B.—THE PROVISIONS FOR COMPENSATION, AND THEIR EXTENT.

It was at first believed for many years that compensation was provided in the peculiar properties of the hæmoglobin. Bohr supposed that hæmoglobin was not a single substance, but was composed of numerous different hæmoglobins, each with its own quotient of O_2 saturation. He described as the specific oxygen capacity of the hæmoglobin that variable quantity of oxygen which it takes up at 15° C. and under a partial pressure of 150 millimetres of mercury per gramme of the iron it contains. This hypothesis renders intelligible the fact that Pflüger's law holds good even when the supply of oxygen is very small, as it is in the severe anæmias. It has also been supported by Abrahamson (9), Haldane, Tobiesen, and Biernacki, among others. Biernacki suggests that a second factor assists in the compensation; in addition to the hæmoglobin, certain other compounds of variable constitution and quantity, the fibrin-

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formers, are supposed to circulate dissolved in the blood, and to possess the power of uniting with O_2.

Hufner (10), on the other hand, opposed Bohr's views from the outset in his well-known researches on the combining capacity of hæmoglobin. He explains Bohr's discoveries by assuming that the apparently different hæmoglobins are no more than mixtures of oxyhæmoglobin with its decomposition products—such as methæmoglobin. The very careful analyses of Kraus, Kossler, and Scholz (11), make it quite plain that hæmoglobin does not possess a variable combining capacity, and Hufner (12) has again definitely negatived the idea in his latest publication. But there is no reason for supposing that the gas analyses upon which Bohr based his hypothesis of the specific O_2 capacity of hæmoglobin are incorrect. It is clear, however, that they must be explained in some other manner, and so they possess an interest not for the anæmias only, but also for the cardiac and pulmonary disorders.

Hufner's hypothesis that hæmoglobin and oxygen combine to form a fairly stable compound which has a small dissociation tension was then attacked by Loewy and Zuntz. These workers found that unaltered blood took up much less O_2 than do either laked blood or hæmoglobin solutions. At 35 millimetres O_2 pressure the hæmoglobin was only 77 per cent. saturated (Hufner 93 per cent.); at 25 millimetres it was only 65 per cent. saturated (Hufner 91 per cent.). They also observed that great differences in the percentage of hæmoglobin saturated with O_2 at one and the same O_2 pressure might be found in different persons and animals. Loewy is of the opinion that individual variations in the tension of dissociation of the oxyhæmoglobin produce this result.

Bohr himself recently (14) noticed that the O_2 taken up by the blood at uniform O_2 tensions varied with the CO_2 tension; when the latter is high the amount of O_2 taken up is distinctly less. This effect is most noticeable at low O_2 pressures; at atmospheric O_2 pressure the O_2 taken up is only slightly lessened by very high CO_2 pressures. Bohr concludes from this that the increased CO_2 tension in the capillaries alters the curve of the O_2 tension in such a way that the absorption of a given quantity of O_2 raises the O_2 tension of the blood to an abnormal degree, thus increasing the concentration of the O_2 in the plasma. Hence it is the increasing CO_2 tension that keeps up the concentration of the O_2 in the plasma, which tends to diminish as the oxygen is used up in the tissues. It is clear, therefore, that although the chemical properties of hæmoglobin are not specially designed to meet deficiencies of O_2, they are of such a kind as to prevent the O_2 tension in the fluids that nourish the body from falling too low. Exactly what happens in diseases of the heart and lungs has not yet been investigated.

A second compensatory provision might be found in the glandular functions of the lungs. It is well known that Bohr denies that the gaseous interchanges in the lungs take place by simple diffusion; he regards the lungs as glands secreting gas, and comparable to the swimming-bladder of fishes. His view has recently received confirmation from several sources: thus Haldane and Lorrain Smith (16) find that the O_2 tension may sometimes be less in the alveolar air than it is in the blood, while

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Magnus (17) has demonstrated that the lungs give no passage to ammonia. But there is nothing in the literature to lead one to see any provision for compensation in the glandular functions of the lungs.

On the other hand, Kraus (18) is very positive that the strikingly lower value of the respiratory quotient observed in some of his cardiac cases while completely at rest would rather lead to the assumption that there was greater difficulty in the excretion of CO_2 from their lungs. He also sees in this disability of the lungs a characteristic peculiarity of the pathological dyspnœa of cardiac patients with failing compensation, for, although the O_2 is supplied under favourable conditions of tension and in sufficient quantity, the blood in dyspnœa is neither able to take it up from the pulmonary alveoli nor to eliminate CO_2 in corresponding amount. According to this, it appears that disturbances in nutrition of the alveolar epithelium are inclined to affect the gaseous exchange in an unfavourable sense. Therefore under no circumstances must compensation be looked for by the development of any such secretory function of the lungs.

The compensation which might arise through the breathing in dyspnœa may now be discussed. With this object in view we must begin by examining in what way dyspnœa originates in diseases of the heart and lungs, and afterwards see what consequences may result for the circulation and the respiratory exchange. For information upon these points analyses of the gases in the blood on the one hand, and of the air breathed on the other hand, must be reviewed. Unfortunately very few of the former exist, and analyses dealing with human arterial blood are entirely wanting for obvious reasons; hence, on this point, the results obtained by experiments on animals are alone available. There are also but few analyses of human venous blood. But many investigations have been made as to the gaseous exchanges in respiration, and important conclusions may be drawn from them. Loewy and von Schrötter (19) describe a most ingenious method of measuring the exchange of gases in the alevoli, and, by means of this, the tension of the gas in the blood.

The method is this: A tube which has a collapsible indiarubber bag affixed near its lower end is led into a branch of a bronchus. When the bag is blown up, this branch is shut off; it is then possible to investigate the breathing in those parts of the lungs which are not, as well as the air in the part that is shut off (see also Haldane's method, *Journal of Physiology*, vol. ii., 1905). The experiments were made on patients with stenosis of the air-passages (some had been tracheotomized). The greater number were in a normal condition as to heart and lungs. One patient was examined who had a compensated heart-lesion and one who had slight emphysema.

The former determinations of Loewy and von Schrötter[1] need not yet be considered, therefore, for the pathology of metabolism. Among the important physiological results may here be mentioned the fact that the O_2 tension in venous blood, with the body at rest, was found to be 5·3 per cent., or 37·5 millimetres Hg. In man the venous blood is

[1] A Loewy and von Schrötter, "Investigations on the Circulation of the Blood in Human Beings" (*Ztschr. f. exp. Path. u. Ther.*, 1905, i. 197).

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saturated with 60 to 65 per cent. of the amount of oxygen which might be taken in from the atmospheric air. The CO_2 tension in venous blood with the body at rest was determined to be 6 per cent., or 42·2 millimetres Hg. The amount of arterial oxygen used up by the tissues was 34 per cent. of the total; out of the 19 c.c. of oxygen present in 100 c.c. of blood, 6·5 c.c. were consumed.

Considering next the purely mechanical relationships in inflammatory diseases of the lungs, there are generally areas in which the ventilation and the circulation of air in contact with the capillary vessels are well kept up, and other parts in which they are limited or even absent. For instance, in bronchitis, the mucus secreted obstructs a number of small bronchi more or less thoroughly, and the areas of alveoli concerned are thus insufficiently ventilated. The blood which flows from them is not duly arterialized. It mingles with other blood coming from well-ventilated areas of alveoli. But even this blood will hardly contain more oxygen than is normal, as hæmoglobin is very quickly satiated with oxygen. The mixture of these two streams of blood results in a decrease of O_2 and an increase of CO_2 in the blood of the left side of the heart. These conditions lead to increased activity on the part of the respiratory centre, and deepen and accelerate the respiratory movements. But this augmented activity does little or nothing for the ill-ventilated areas; the obstacles which impeded the exchange of air in the diseased places—plugs of mucus, for example—have to be overcome by more powerful ventilation. On the other hand, if the parts which were already well ventilated obtain still more air by the increased respiratory movements, called into play by the respiratory centre, the following curious condition is the result: that portion of the lungs in which the current of air chiefly circulates breathes in an exaggerated way, while the other portion remains almost inactive. As the gases exhaled come chiefly from those parts where the breathing is exaggerated, their composition is naturally the same as that always found in the gases exhaled in forced breathing. They are richer in O_2 and poorer in CO_2 than the average gases exhaled by the lungs in health. This statement of Geppert's holds good for the greater number of lung diseases—at least, as far as concerns the O_2. The CO_2, on the other hand, seeing that the blood is sometimes comparatively overloaded with it, is occasionally excreted in larger quantities, just as it is in ordinary overactivity of the lungs.

Existing investigations into the gases of the blood and the gaseous exchanges agree well with this. For instance, Sackur (21), in his examinations of the tension of the gases in the blood, found that when pneumothorax had been established in dogs, the amount of oxygen in the arterial blood sank to almost half of its original quantity. The amount of carbonic acid in the arterial blood, however, varied very little, and the variations were not constant. In half the cases the volume of the CO_2 rose, and in the other half it fell, but to no great extent either way. Sackur thinks that the reasons for this fall are not fully understood. He explains the recorded variations as follows: the amount of CO_2 in the arterial blood occasionally shows marked variations; on the one hand it falls in the more powerfully ventilated, healthy part

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of the lung, and on the other hand there is a failure in the circulation of air in that part of the lung which is not being used for breathing, and these two processes do not balance one another. As to the exchange of oxygen, matters are quite clear. With exaggerated breathing more CO_2 is certainly given off, but practically no more O_2 is taken up. It is interesting to know that Sackur observed the same changes in the tension of the gases in the blood when the pressure of air was reduced to one quarter of an atmosphere; the disturbance of the respiration was then of the same type as in pneumothorax.

Since the results of Sauerbruch's investigations have been published, more attention has begun to be given to the mechanical disturbances of breathing in pneumothorax and to the pneumatic chamber.[1] Sauerbruch himself, after his experiments, subscribed to Sackur's opinion that the collapsed lung has more blood flowing through it than the healthy one, because its vessels are wider open. As a proof that this is a correct assumption he adduces the fact that when the collapsed lung is blown out, and the bronchus shut off, the existing dyspnœa improves or disappears, because by this means more blood passes through the other—the breathing—lung.

According to this account the compensatory increase of work demanded of the healthy lung would be further added to by its faulty supply of blood, and dyspnœa would only arise through central stimulation of the respiratory centre. In opposition to this, Hofbauer[2] has shown that in the cases of pneumothorax which he investigated, the respiration as recorded by the cardiopneumatograph indicates that the chief difficulty experienced is in expiration.

Hofbauer attributes the distressed breathing of pneumothorax to the fact that, owing to the entrance of air into the thoracic cavity, both lungs have greater possibilities of retraction than is ever the case under ordinary circumstances. Hence a substantial portion of the elastic energy which normally expends itself on expiration is withdrawn, and difficulty in breathing consequently ensues. It is as well to add in justification of this conception that, in pneumothorax, the respiration of the healthy lung is thus also impaired; the observations made by Murphy go to prove that, after unilateral pneumothorax is established, the difficulty in breathing decreases if the mediastinum is fixed. On the other hand, it is well established that in pneumothorax exaggerated breathing is observed, and that the one lung able to breathe deals with the same volume of air as both lungs did before.

From analyses of the gases of venous blood the following figures may be cited. Working under Kraus, Kossler found that in various diseases of the lungs the amount of CO_2 in human blood rose during dyspnœa (22). Kraus himself writes: "There is an entire absence of analyses of venous blood in emphysematous patients. Nobody doubts that their blood is richer in CO_2."

[1] Sauerbruch, "On the Pathology of Pneumothorax, and the Basis of my Experimental Reduction of it" (*Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, xiii. 399).

[2] Hofbauer, "Mechanism of the Disturbances of Respiration in Diseases of the Pleura." (1) "Dyspnœa in Pneumothorax" (*Ctb. inn. Med.*, 1905, Nr. 6). Hofbauer, (2) "Causes of Disturbances of Breathing in Pneumothorax" (*ibid.*, 1905).

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In opposition to these statements, Gréhant and Quinquaud (23) found in a case of artificial pneumonia, produced by the injection of silver nitrate solution, that the amount of CO_2 in the venous blood was lessened. It will be necessary to discuss this result further at a later stage, as from this one experiment these authors inferred that in pneumonia the general internal production of CO_2 decreases—a far-reaching conclusion which is most certainly incorrect. Kraus (24), too, gives an example which contradicts this hypothesis of Gréhant and Quinquaud. In a case of febrile pneumonia he was unable to establish any decrease in the amount of CO_2 produced, though such a decrease is usually a characteristic of fever, "probably," he says, "because, on account of the extensive inflammatory infiltration, the lungs experience difficulty in giving off the CO_2." No examination has been made of the amount of oxygen in the venous blood here, but it is probable that it is insufficient; at any rate, Sackur has already found the amount of O_2 in arterial blood to be much diminished.

Krehl believes that the mere fact that cyanosis is found in lung cases where the circulation is not retarded suffices to prove the presence of greater quantities of reduced hæmoglobin in the blood (25). But this conclusion does not seem to me quite certain, because the blue colour, —such as veins show, for instance—is not necessarily caused by the venosity of the blood, as Brücke suggests, but is due to the semi-opacity of the vessel wall.

So much concerning the gases in the blood. As for the investigations of the gaseous interchanges in cases of lung disease, they all accord with Geppert's statement that exaggerated respiration occurs in the healthy parts of the lung. It was frequently found that the whole amount of air respired was above the normal. In emphysematous patients Geppert himself found figures habitually above the normal. If he himself considered them to be normal, it must be attributed to the fact that, in his day, no proper standard had been established with which they could be compared, as Kraus very justly points out. Further results were obtained by Pick's experiments in various diseases of the respiratory organs, tuberculosis, pneumonia, and pleurisy (25). He found that the amount of air respired was normal, or more than normal, although the vital capacity was diminished. Winternitz observed that the volume of the respired air increased in cases of advanced tuberculosis which were free from fever (27). Experiments on animals led to the same results. Thus Sackur saw, after pneumothorax had been established, that the one lung able to breathe dealt with almost the same volume of air as both together normally did, a fact endorsed by Vaughan Harley (28). In the same way Loewy (29) and Gréhant and Quinquaud found that the volume of air breathed in was increased in cases of artificially produced pneumonia. Geppert's conclusions as to pulmonary dyspnœa—viz., that in lung diseases exaggerated respiration is set up by way of compensation—may be fully accepted.

The comportment of dyspnœa in cardiac cases must now be considered. It might be imagined—and the first edition of this book gave it to be understood—that no difficulty would be experienced here in

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ventilating the lungs. Indeed, it was rather supposed that under all circumstances the blood flowed into the left ventricle sufficiently arterialized, because, even if the flow into the lungs were delayed, that would only cause improved oxygenation. The cyanosis and the dyspnœa in these patients would not then depend upon the condition in which the blood left the lungs, but would have to be attributed solely to the delay of the blood-stream in the greater circulation, by which the oxygen contained in the arterial blood would be more completely used up.

According to this supposition it would naturally follow that dyspnœa is purely central in origin. However, even supposing that this practically is the case, the conditions are not really so simple and transparent.

In most diseases of the heart the lesser circulation sooner or later becomes congested, and this leads to increased pressure and to delay in the flow of blood. Therefore the question arises whether increased pressure and delay might in any way lead to disturbance of the conditions of its aeration. Given a closed system of tubes containing fluid which is charged with one gas, and able to exchange this gas for another by diffusion through a semipermeable membrane, no physical investigations have yet been made to determine whether a rise in the hydrostatic pressure would influence the gaseous interchange then occurring. Professor Straubel, a physicist whom I questioned on this point, told me that, speaking theoretically, no impairment of the aeration would be likely to ensue from increased hydrostatic pressure. Clinical experience on this question is not uniform, and opinions differ. Romberg (30), for instance, thinks that an increase of the pressure in the lesser circulation, such as that occurring in compensated mitral disease, or the diminutions of that pressure which occur when the right ventricle acts feebly but the lungs are not diseased, cause no dyspnœa.[1] Krehl, on the other hand, has repeatedly drawn attention to the disturbed respiration caused by the increased blood-pressure. Especially does he insist—and here von Basch (32) agrees with him—that aggravated dyspnœa in which high pressure and delayed circulation are present, paradoxically enough diminishes in the same measure as the action of the right chamber weakens, thereby causing the blood-pressure to fall. Nothing is known about the influence of the delay of the circulation upon the exchange of gases. Romberg, however, remarks how very much respiration depends upon the velocity of the circulation, and also, though in a less degree, upon the amount of the simultaneous flow of blood. He concludes that a slowing of the circulation might perhaps reduce the vital processes in the epithelium of the alveoli and the endothelium of the capillary vessels, and thus affect the secretory function of the lungs. It is clear that at present these simple questions cannot be answered, and until analyses of arterial blood in diseases of the heart have been made no answer to them will be forthcoming.

But quite apart from this, von Basch and his pupils have disputed

[1] Hering, too (30A), observed that when he clamped off the arch of the aorta in rabbits, a noticeable hyperæmia of the lungs occurred. But the animals while breathing naturally and at rest showed no dyspnœa. Only a decrease in the depth and frequency of their respiration was observed. At the same time the animals were able to breathe deeply, and did so when they moved, for example.

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the statement that the ventilation in the lungs is not impaired in heart disease. Long before von Basch, Traube, as also Cohnheim and Fraenkel, had insisted that when the pressure was increased and the vessels of the lungs were overfilled with blood, the capillaries bulged out into the alveoli and diminished their cubic capacity.

Von Basch next asserted that this was a wrong idea, and that the capacity of the alveoli must rather be increased, since the vessels were stretched by the larger quantity of blood in them. Hence, he said, the whole of the pulmonary tissue must stiffen; an erectile swelling of the lung-tissue would ensue, and would impair respiration by impeding the excursions performed by the lungs during breathing. Thus the essential factor in the dyspnœa of cardiac as of pulmonary disease would be the enhanced difficulty in breathing, leading to insufficient aeration in the alveoli.

Von Basch's views have been copiously defended in many works by his pupils, Grossmann (33) and Zerner (34). They were attacked, especially on the experimental side, by Einthofen (35) and von Löwit (36). They commend themselves little to clinicians, because such rigidity of the lungs is rarely met with in the sick-room. Cardiac asthma affords an exception to this rule, and Fraenkel (37) believes he has demonstrated that here a swelling does take place in the lungs. This has not yet been proved, however. I myself have often looked for it in cardiac asthma, but always in vain. Still, it must be admitted that von Basch's experimental results are a great help, though they cannot be directly transferred to human pathology. This is all the more the case, since in Kraus's well-known work, "The Strength of the Constitution as measured by Fatigue," a number of observations on diseased persons are given which accord very ill with von Basch's views. Kraus (38) demonstrates, by means of experiments on respiration, that in the marked dyspnœa of cardiac patients with failing compensation the pulmonary aeration is not diminished; indeed, over-ventilation, more especially as regards the taking up of O_2, is characteristic of this form of dyspnœa too (38). In none of his patients, even with advanced exhaustion and dyspnœa, was the power of deep breathing diminished, so that the consumption of the air respired was more complete. This exaggerated respiration and hyperventilation clearly tell against von Basch's theory of the rigidity of the lungs.

Kraus's statement has lately been confirmed in another way by Hofbauer, who, in a series of stethographic experiments, examined a severe case of cardiac dyspnœa (38). Here he found that the curve of the respirations, as recorded by a Marey's cardiopneumatograph, gave evidence of active and deep thoracic respiratory movements, and rose at an acute angle. When digitalis was given improvement followed, and the curve at once became flattened out. The movements of the thorax and the expansion of the lungs are therefore more ample before the use of digitalis than after; in other words, dyspnœa is not determined by rigidity of the lungs.

Hofbauer, on the other hand, recorded the movements of the thorax graphically in a case of cardiac asthma, and found the curve of the

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respiration flattened, and therefore changed in a sense congruent with von Basch's views. In these cases, in which the right ventricle exerts itself to make up for some obstruction or faulty action in the left ventricle, and in which, therefore, there is not likely to be any delayed circulation in the vessels of the lungs, the first thing to be noticed is an overfilling of the pulmonary vessels. These are the cases to which von Basch's theory is most applicable.

To sum up, it may be concluded from Hofbauer's statistics from human beings that there are different types of respiration in cardiac asthma and cardiac dyspnœa, and that in the special case of asthma von Basch's views may be right.

The analyses of the gas in the venous blood made by Kraus in heart disease are both interesting and valuable. According to Kraus, the average volume of CO_2 in the blood of the median vein in man is somewhat over 30 per cent. In local stasis—for example, in ligature of the limb—it may rise as high as 70 per cent. In cases of heart disease with cyanosis, during repose the amount of CO_2 varies from 30 to 56 per cent.; that is to say, on an average it is half-way between the normal and the highest possible value. Under physiological conditions, when the muscles are at work, the CO_2 content of the blood sinks perceptibly below the normal mean—that is to say, as low as 26 per cent. This is because the acidification of the blood, as well as the increased activity of the heart and lungs, do more than compensate for the marked increase in the CO_2. Therefore, in cases of heart disease the amount of CO_2 in the blood is already much increased with the body at rest; it rises to as much as 38 per cent. in the dyspnœa caused by violent muscular exertion, a proportion far exceeding that found in healthy persons when at rest. From this Kraus rightly draws the following conclusions: "that persons suffering from heart disease hold back CO_2 even during muscular repose; as soon as the CO_2 production increases they are unable to prevent its accumulation in the body, although the organism exerts all its excretory mechanism to the utmost."

It is interesting, too, to know that Kraus found a marked diminution in the amount of oxygen in the venous blood of cardiac patients during muscular exertion; and it is especially to be noted that Kraus is not inclined to attribute this to the fact that the O_2 is more quickly used up. For, though Finkler had already ascertained that the difference in the O_2 contained in the venous and the arterial blood increases in the very proportion in which the speed of the blood-stream increases, yet Kraus does not think it likely that a retardation of the circulation is followed by any appreciable improvement in the consumption of the oxygen. The reason he gives is "that even in a healthy man the O_2 in the venous blood does not decrease in amount during exertion, and it is not legitimate to conclude that the tissues seize on the oxygen of the arterial blood with greater avidity. It is more reasonable to suppose that the increased demands of the tissues for O_2 are met by a larger activity on the part of the heart, which propels a correspondingly greater amount of blood round the circulation."

The question can only be decided by the estimation of the O_2 in

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arterial blood. But Kraus is convinced that it is probable that the taking up of O_2 is also disturbed in cardiac cases. Such disturbance will be readily understood when one considers that to begin with these cases are frequently anæmic, and, further, that coarser or finer indurative changes in the lungs may hinder the gaseous exchanges. For this process Kraus has coined this very precise phrase—"that the lungs perform a more important function as bellows than as an organ for the absorption of O_2 and the excretion of CO_2." Of course mechanical hindrances may disturb respiration in heart disease quite apart from actual inelasticity of the lungs.

Any considerable enlargement of the heart may *per se* serve to cramp that organ; in the same way, fluid exudates may compress the lungs. Such compression, however, would probably involve the same consequences for the respiration as have already been cited above in the case of pneumothorax.

It is therefore apparent that, with the single exception of rigidity of the lungs in the case of cardiac asthma, dyspnœa shows exactly the same symptoms in diseases of the lungs and of the circulation. In both cases there is hyperventilation, and dyspnœa must be looked upon as "a reaction of the centre for respiration, due to a condition of increased excitation by the circulation" (Kraus).

There is still some dispute as to the method of this excitation. The recent work of Plavec leads to the conclusion that want of O_2 and accumulation of CO_2 stimulate in different ways, and that in any case the presence of CO_2 in the blood is a normal stimulus to respiration (39).

The question still remains as to how far the action of the heart and of the vessels may serve to compensate for the impairment of the supply of O_2. It is easy to see that the quicker pulse and more violent beating of the heart generally to be observed in diseases of the lungs and heart cause an increase in the circulation of the blood. Kraus has investigated the rapidity of the flow of blood by means of von Kries's method employing the flame-tachogram. He has found that, both in healthy persons and in those whose hearts are diseased, bodily work and the shortness of breath it produces affect the tachogram in such a way as to point to a clear increase in the difference between the velocities of the venous and the arterial blood-streams. From this, and from the fact that, under like conditions of investigation, the pressure of the arterial blood was found to be higher, Kraus concludes that the action of the heart becomes more vigorous.

Except for this, there exists little experimental material on the subject. Bayliss found that with Ringer's solution saturated with CO_2, the velocity of the flow rose in one isolated extremity (40). In the same way Rebustello, who established artificial circulation in the hind-leg of an animal, noted that the asphyxia excited the vasoconstrictor centres of the skin and muscles no less than it did those of the other tissues (40).

Reviewing all that is known as to the adjustment of compensation, it is evident (1) that compensation can be established in the capillary blood by the dependence of the tension of the O_2 upon the coexistent tension of the CO_2; (2) that the hyperventilation of the lungs which

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ensues, together with the increased action of the heart, set up a regulating mechanism which acts very promptly; but that (3) it can be proved that the blood is overloaded with CO_2 in diseases of the heart or of the lungs.

C.—THE QUANTITATIVE CHANGES IN THE METABOLISM.

After what has been said about compensation in the previous sections, little surprise will be felt should the results of quantitative investigations of the metabolism prove on the whole to be negative. No direct calorimetric determinations exist, but indirect ones of the gaseous exchange, both in human beings and in animals, have clearly shown that the very substantial hindrances to the gaseous exchange are so well compensated that in the end a diseased person uses up as much O_2 in his tissues in a given time as a healthy one does. The older works by Hannover (42) and Moeller (43) show the same results.

Moeller's examples may be given here because he did not rest content to take only samples of the air, as has been the practice of more recent observers, but made his patients breathe for as much as six hours in a large Pettenkofer's apparatus.

The patients gave off CO_2 per kilogramme of their body-weight and per hour as follows:

	Gm.
1. Pleuritic exudate (up to the second rib)	0·532
2. Pleuritic exudate	0·482
3. Pleuritic exudate after recovery	0·486
4. Pleurisy in convalescence	0·622
5. Emphysema	0·450
6. Pulmonary phthisis	0·543
7. „ „	0·612
8. „ „	0·565

Moeller's normal values should be given for comparison; they varied from 0·437 to 0·633 gramme. The normal values in fasting and repose which have lately been discovered are considerably less. Magnus-Levy and Falk, for instance, consider that healthy middle-aged men of medium weight consume 3·41 c.c. of O_2 per kilogramme and minute = 0·292 gramme per hour and kilogramme; and they produce 2·77 c.c. of CO_2 per kilogramme and minute = 0·327 gramme per hour and kilogramme, the normal values.[1]

Geppert (20), Loewy (29), Kraus and Chvostek (44), Quinquaud (45), Speck (46), Riethus (47), Svenson (48), Robin and Binet (49), and finally Winternitz (27), have all lately given further accounts of the respiratory metabolism in heart disease. But many of their results are open to dispute, inasmuch as most diseases of the respiratory organs are febrile, and, supposing their investigations to have been made at a time when the patients were free from fever, the latter can only be looked upon as convalescent from the foregoing fever.

In the case of convalescents after prolonged fever, Svenson has

[1] Leo (*Zt. klin. Med.*, xix.) gives for fasting human beings when at rest a mean value of 3·08 c.c. CO_2 and 3·81 c.c. O_2; Magnus-Levy (*Kongr. i. Med.*), CO_2=2·3 to 3·5 c.c., O_2=2·8 to 4·5 c.c. (see Vol. I.).

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ascertained that a marked decrease of oxidation follows immediately upon the feverish period; in consequence of this, the metabolism becomes more vigorous, and even surpasses its normal standard. Further, the changes observed must not in all cases be attributed to obstruction of respiration only. For example, in cases of pneumonia, after the crisis, where the lungs still contain unabsorbed exudate, this still has to be absorbed; in afebrile phthisis, toxic decomposition of the tissues, set up by infection, may occur even during the afebrile period. And there is yet another difficulty which especially interferes with the measuring of metabolism in disease. It is known that respiration varies considerably according to temperament and constitution, whereas the metabolism of each individual is remarkably constant. Confronted with a sick man, we are ignorant of what his metabolism may be when he is sound, and investigations made whilst he is recovering will not fill the gap. Hence it is plain that only constant and tolerably large variations from the mean values must be employed for the deductions of conclusions that are to be trustworthy.

Geppert and Speck record analyses of the metabolism in *emphysema*. In Geppert's four investigations the amount of CO_2 given off varied between 2·64 and 3·48 c.c. per kilogramme and minute—that is, between 0·31 and 0·41 gramme per kilogramme and hour; and the consumption of O_2 varied between 3·6 and 3·93 c.c. per kilogramme and minute—that is, 0·31 and 0·38 gramme per kilogramme and hour. Speck's figures for CO_2 were 3·8 and 4·43 c.c. per minute and kilogramme, and for O_2 3·4 and 4·8 c.c.

Speck's figures are quite normal; those of Geppert somewhat low, but, if compared with those established by Magnus-Levy and Falk for persons of the same age, they too appear to be normal. It is of interest to note that Geppert's figures rose somewhat when the patient had bronchitis, increased compensation being then necessitated.

Few analyses exist for *pneumonia*. Riethus found a marked decrease in the consumption of O_2 after the crisis.

First day	temperature	40·0° C. = 7·9 c.c. O_2	per	minute	and	kilogramme.	
Second	,,	,,	36·1° C. = 5·5	,,	,,	,,	,,
Third	,,	,,	36·1° C. = 4·7	,,	,,	,,	,,

Svenson, examining two cases of pneumonia in recovery, put down the figures ascertained after the lapse of weeks (18 and 49 days) as the normal value for these patients, and, comparing this with the values on the first day after the crisis, found an increase in the proportions of 17 per cent. and 29 per cent. After this the metabolism fell to the normal standard, or even lower, and later, in the second week, rose again from 8 per cent. to 14 per cent. In convalescence after typhoid fever, Svenson found the variations were similar, only more marked; at first there was a period of low values, which was followed by one of higher values. We are not here concerned with Svenson's deductions as to the decomposition of tissues in convalescence (the increase of the respiratory quotient in consequence of the putting on of fat, reduced values viewed as signs of exhaustion, etc.). Shortly after the crisis, at a time when the infil-

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tration was still present, Svenson and Riethus both observed somewhat higher values, which are to be explained by the increased work of respiration, partly, too, by the process of absorption itself. Very interesting is the case of a patient recovering from pneumonia who was made to do work. He worked more economically than a patient recovering from typhoid fever, who was examined at the same time, the figures being 1·50 as against 2·70 c.c. O_2 per kilogramme and minute of work. Whilst the typhoid patient was able to recoup himself for the extra consumption of O_2 by more violent respiration, the pneumonia patient must have made better use of the air he absorbed as he worked, and his respiratory quotient also rose.

Gréhant and Quinquaud made an extraordinary statement as to the influence of *pleurisy* on respiratory metabolism. In a case with a large pleural effusion they found that CO_2 was given off in smaller quantities, down to one-sixth of its normal value. After tapping, the amount of CO_2 increased fourfold, and only regained its normal level after complete absorption of the fluid. Bronchitis set in, and it sank 50 per cent. This result directly contradicts that of Möller cited above. It is the same with other experiments of Gréhant and Quinquaud in other diseases. In two cases of pneumonia and one of emphysema, at their acutest stages during the fever, they found an extraordinarily marked decrease in the CO_2 given off—to about one-third in the emphysema and to one-quarter in the pneumonia. All the trustworthy German investigations given above so absolutely contradict this that it must be presumed that their results are entirely wrong.

Tuberculosis of the lungs has been most thoroughly examined. Of the older observations, those by Hannover, Gautier and Regnard may be mentioned, also the values by Möller, already cited (49, 50, 51). Loewy and Kraus, employing better methods, have made more recent analyses in febrile and afebrile cases of tuberculous disease. The values obtained do not substantially differ from the normal; in a few cases only they were higher. Still, even in phthisis without fever, Loewy occasionally found average values exceeding the normal. In the same way, Riethus sometimes found higher values in tuberculosis, even when there was no fever—namely, 6·2 c.c. for the consumption of O_2; 5·3 c.c. for the giving off of CO_2; also 5·9 c.c. O_2 and 4·9 c.c. CO_2. Riethus attributes this, and the higher figures recorded by Loewy in like cases, to the influence of the infection as such. Krehl and Soetbeer, in their experiments on cold-blooded animals, also remarked that infection as such may lead to increased decomposition of the tissues.

In Loewy's investigations it was remarkable that an abnormally low respiratory quotient was sometimes observed in advanced phthisis. He attributes this to the existing state of inanition. Quinquaud found varying conditions—for instance, in advanced stages, even quite independently of fever, an increase; at other times he found normal values. In rather less advanced cases, in which, however, emaciation and debility were evident, the values in one and the same afebrile patient varied from 3·13 to 7·45 c.c. CO_2 per kilogramme and minute. Speck, in a chronic afebrile case, found the consumption of O_2 4·35 c.c., and the output of

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CO_2 3·85 c.c. per kilogramme and minute. In another acute case the values varied, but were higher than the normal limits—about 6 to 5 c.c. for the O_2 and 5 to 7·3 c.c. for the CO_2. The last investigation made by Winternitz, showing clearly that the metabolism of phthisis does not usually vary much from the normal, may here be given *in extenso*, as it entailed much comparative analysis. A healthy man and a man in advanced phthisis, of about the same weight and constitution, were the subjects of investigation.

	Frequency of Respirations.	*Extent of Respirations.*	O_2.	CO_2.	O_2.	CO_2.	*R.Q.*
		C.c.	C.c. per Minute.		C.c. per Kg. and Minute.		
Healthy man, thin, 50 kilogrammes. Spirometer value 3,400 c.c. ..	16	5,128	202·1	156·6	4·04	3·13	0·77
Case of tuberculosis, 51 kilogrammes. Infiltration and cavitation of right upper lobe, infiltration of left apex, bronchitis in left lower lobe. Thin, afebrile, spirometer value 2,500 c.c.	19	6,483	226·3	188·9	4·43	3·70	0·83

The only authors whose statements differ essentially from those already quoted are Robin and Binet, who in numerous cases of phthisis constantly found a marked increase in the gaseous exchanges of the respiration. They came to the conclusion that in tuberculous patients—

1. The amount of air inhaled by women rises on an average 110 per cent., that of men 80·09 per cent.

2. The amount of CO_2 per kilogramme and minute rises in women 86 per cent., in men 64 per cent.

3. The consumption of O_2 in women rises above the normal to the extent of 100·5 per cent., in men about 70 per cent.

Robin and Binet observed this enlarged metabolism not only in tuberculous persons, but in cases which they describe as being in an *état protopathique*, or as an *état de déchéance prétuberculeuse*, and to which they therefore attribute a *vitalité exaspérée* in contradistinction to the *vitalité amoindrie* previously supposed to exist. Robin and Binet have so far only published their results somewhat briefly, so that it is not possible to criticise them in detail (49). Parkinson (*Practitioner*, 1906) comes to the same conclusions, and contends that the fact holds good for the descendants of tuberculous individuals, and may be used for diagnostic purposes. Hauser (52) agrees with them also, but makes a most mistaken attempt to prove that the increased respiratory metabolism in tuberculous persons, or those disposed to be consumptive, is to be explained by the impaired action of the heart, which causes the blood to linger longer in the capillary vessels.

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On the whole one may pin one's faith to Winternitz, relying on the investigations already to hand as to the processes of metabolism in phthisis. His conclusions are the following: In chronic tuberculosis of the lungs, as long as the conditions of nutrition are good, the consumption of O_2 and the giving off of CO_2 keep within, the normal limits. In advanced consumption with marked wasting, the values are found to be relatively higher. This must be attributed to the wasting and the relative enlargement of the surface of the body caused thereby, as well as to the increased exertion of breathing. In many cases a further increase of metabolism may be observed. Winternitz estimates it at 10 to 20 per cent., and attributes it to toxic decomposition of protein; but Krehl and Riethus say it is due to the infection as such. Taking a general survey of all the figures that have been given concerning metabolism in diseases of the respiration in human beings, it is clear that the quantitative analysis affords no basis for the view that the tissues are less active on account of the difficulty the lungs experience in the breathing, and therefore in taking up oxygen—that is to say, they do not consume less than the normal amount of O_2. It is true that no experimental investigations have been made upon patients with lung disease in which they were made to do work up to, or even beyond, the limits of their respiratory reserve power, excepting those of Svenson on convalescent cases of pneumonia, and they have no bearing on the question now before us. For such conditions of extreme difficulty in taking in O_2 one must rather adduce as evidence the changes of metabolism found under marked reduction of the air-pressure and in asphyxia. The facts tabulated by Kraus in his experiments on cases of heart disease are also to the point here. The few experimental investigations made on animals showing a more or less marked impairment of respiration and its quantitative consequences may also be cited. Gréhant and Quinquaud artificially established experimental pneumonia in dogs by injecting a 10 per cent. solution of silver nitrate. They then found that the quantity of CO_2 breathed out sank considerably, and only rose to the normal again when the pneumonia was cured. Loewy repeated these experiments, and found, in his starving dogs, that while the absorption of O_2 increased, the excretion of CO_2 remained unchanged, so that the respiratory quotient fell as low as to 0·46. As the animals had little or no fever, Loewy attributes the increased consumption of O_2 chiefly to the greater exertion of breathing.

Further experimental material exists dealing with the limitations of space caused by fluid effusions. Gréhant and Quinquaud again made the experiment of injecting olive oil into the pleural cavity of animals. After forty-eight hours they observed a marked decrease in the CO_2, and the same thing occurred when they produced pleural effusions by the insufflation of cantharides. Harley, on the other hand, in compressing the lung by means of an indiarubber bag filled with water, found that the O_2 absorption and the CO_2 production both rose. He does not think this can be attributed either to increased exertion in breathing or to fever, or to special efforts of the heart, because the increased excretion continued after the bag had been emptied, supposing the lung

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had first been compressed for some time; on the other hand, if it had been compressed for a short time only, the breathing became normal.

Harley's experiments are sufficiently remarkable, but, as Jaquet has already pointed out, they are not above suspicion. Perhaps there is some error due to the morphine narcosis and the retention of CO_2 caused thereby.

The respiratory metabolism of the dyspnœa caused by section of the vagus has been carefully examined several times [see Esser (53)]. Rauber and C. Voit established the fact that the O_2 absorption and CO_2 production were not changed by division of both the vagus nerves. A work has only just appeared which shows that certain changes which compensate each other do occur. Von Maar, in fact, found that the vagus and the sympathetic nerve effect a change to the following extent (54): The absorption of O_2 increases considerably, and generally is doubled, in the lung whose vagus is cut, and it falls almost as much in the other lung. The excretion of CO_2 was affected in the same sense as the absorption of O_2, but to a far lesser extent. Von Maar found that as soon as the other vagus was divided the breathing of the two lungs became equalized. He exposed and scrutinized the lung during one experiment, and could see no change in the amount of blood it contained, thus making it plain that the circulation has nothing to do with the changes observed. On the other hand, by compressing the left pulmonary artery, he did directly disturb the circulation through the lungs. Partial compression had no effect; complete obstruction caused the O_2 absorption and CO_2 excretion to fall. But the circulation in the left lung was not altogether suppressed, as, according to von Maar, it still got a little blood through the anastomoses. The decreased O_2 absorption of the left lung was exactly compensated for by the increased amount taken in by the right lung, where there was naturally a stronger flow of blood, owing to the compression of the left pulmonary artery. On the other hand, the right lung did not compensate for the decreased amount of CO_2 given off by the left lung. These experiments on impeded circulation of the lungs give von Maar's investigations a special interest for us. As regards the results he obtained by section of the vagus, it must be objected that von Maar did not take into consideration the fact that the bronchi might well be much dilated after the section, and might thus influence the respiration.

There exists another older example, due to Lépine (55), of the effect impeded circulation through the lungs has upon respiratory metabolism. He injected oil into the central end of the external jugular vein of dogs, and then found a considerable decrease in the CO_2 expired, and, allied with it, a decrease of the whole amount of air exhaled. In a parallel investigation in which dyspnœa had been produced by considerable constriction of a cannula placed in the trachea, he found that the total volume of air exhaled was less, but that the amount of CO_2 given off was increased, both relatively and absolutely. We know, of course, from Lichtheim's and von Gerhardt's investigations that animals can endure to have several lobes of their lungs tied off. Rauber, Weil and Thoma have proved, for the case of pneumothorax experimentally produced, that the gaseous exchange is hardly affected (57). Thus far the experi-

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ments upon animals; in considering the qualitative changes we shall have to return to them again.

As regards the metabolism of respiration in heart disease Kraus's excellent work on the subject gives much information, and permits the conclusion that "examination of the respiratory gaseous exchanges of persons with morbidly-retarded circulations gives not the smallest reason for believing that their organic decomposition processes are subnormal during repose."

In opposition to this Kraus found, as has been already mentioned, that the respiratory quotient in some of his cases of heart disease was very low. He explains this by assuming an impaired CO_2 excretion.

The relation was quite different when the patients suffering from heart disease worked till they were exhausted. In all these cases of increased demand for O_2 Kraus was enabled to establish that the supply of it was really insufficient. This was shown partly by the absolute decrease in the maximum amount of muscular work that could be performed, muscular work being a function accompanied by the consumption of much O_2, and partly by a rise in the respiratory quotient not otherwise to be explained. Kraus considers that this rise points to a prolongation of the processes of disassimilation after the function upon which their maintenance depends has ceased to be active — that is to say, partial local suffocation occurs—and he attributes the generation of CO_2 in quantities outdistancing the absorption of O_2 to the consumption of intramolecular oxygen. Kraus found this condition of affairs in healthy persons but seldom, and then only as the expression of extreme exhaustion.

It is important to state that the same condition—namely, the excretion of CO_2 in normal or in increased quantities, with a simultaneous decrease in the absorption of O_2—was found when the air-pressure sank to 350-450 millimetres Hg [the literature is given by Jaquet (58)]. The respiratory quotient rises here, too, when there is a difficulty in supplying O_2 and the intramolecular oxygen is seized upon. The same thing occurs when human beings have to breathe an atmosphere which is at normal pressure, but contains too little O_2.

It does not fall within the scope of this section to consider the extensive literature of this subject. The effects of diminished atmospheric pressure are recorded in Jaquet's chapter on the Therapy of High Altitudes.

The quantitative changes of the metabolism in diseases of the heart and lungs given above may be summarized as follows; :

1. No diminution of the metabolism by a limitation of the decompositions or of the consumption of O_2 can be found.

2. Excepting under critical conditions, the intake of O_2 and the output of CO_2 usually vary within the limits of the normal, if, indeed, they do not show a compensatory increase. In the infective processes the infection can occasion a further augmentation of the metabolism.

3. In the worst cases of heart disease, and when the supply of O_2 is much diminished artificially, the intake of O_2 becomes inadequate. Under these circumstances the consumption of intramolecular oxygen may be observed.

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D.—THE QUALITATIVE CHANGES IN THE METABOLISM.

Investigation of the gaseous interchange can give but little information as to the qualitative changes in the metabolism. It is well known that the respiratory quotient indicates the nature of the decompositions that take place—viz., how much protein, fat, and carbohydrate are being broken down. It does this only on the supposition that the exchange of gases between the blood and the air in the lungs remains intact; but it has been shown that in cardiac and pulmonary disease this is hardly the case. Hence the respiratory quotient affords no help in determining the finer qualitative alterations that occur; and this is especially true of the production of the incompletely oxidized substances known as the intermediate products of the metabolism. It has been already mentioned that in the worst cases of heart disease the intake of O_2 is hindered, and that the respiratory quotient rises because of this deficiency, so that all the statements made in the preceding sections about the respiratory quotients must be considered together. In patients with pulmonary disease the respiratory quotient has generally been found to be normal. This is the case in the figures given by Geppert and Speck for emphysema, by Möller for pleurisy, and by a number of authors consentaneously for tuberculosis.

There are other investigations which indicate an alteration in the respiratory quotient, but care must be exercised before conclusions are drawn from these. Various objections have been raised against calculations of the respiratory quotient based merely on the examinations of fractions of the respired air, and quite properly. It also appears that in all infective processes the intake of O_2 and the simultaneous output of CO_2 may vary far more widely than they do during health, a fact upon which Riethus lays especial stress. Thus a great diminution may be observed in the respiratory quotient in the infections, including, naturally enough, the infectious disorders of the lungs. It is, perhaps, necessary to emphasize the fact that this diminution is not due to the fever. It is not determined by the onset and ending of the fever, but, as Riethus expressly states, it is the infection as such that lowers the respiratory quotient. This having been set forth, the figures found for the respiratory quotient can be properly appraised. In lobar pneumonia Riethus determined the following figures: During the fever the respiratory quotient was 0·67; one day after the crisis, 0·70; one day later, 0·85. Corresponding figures were found by Svenson in two cases of lobar pneumonia:

	Case I.	*Case II.*
During fever period	0·702	0·700
First day after crisis	0·706	0·705
Four days later	0·832	0·769
Ten days later	0·969	0·907

The values during convalescence are surprisingly high, and Svenson suggests that they indicate a putting on of fat, CO_2 being split off from the molecules of carbohydrate and fat being formed. If this were the case

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the respiratory quotient would be increased by a rise in the output of CO_2 rather than a fall in the intake of O_2.

Very low respiratory quotients have been found in experiments upon animals, as has been already indicated. Gréhant and Quinquaud, and also Loewy, produced artificial pneumonia by the injection of $AgNO_3$ solution. Loewy found that the quotient fell as low as to 0·46 in the dog. Gréhant and Quinquaud determined the output of CO_2 only, and their statement, perhaps, need not be regarded as final. It has been already stated that these authors also found unusually low values for the CO_2 in various human pulmonary diseases, in contradiction to all the German investigations. But no objections attach to Loewy's experiments. It appears that the respiratory quotient of his dogs fell though fever was absent, so that the consumption of O_2 was increased, while the excretion of CO_2 remained low, and was relatively lessened.

It is far from easy to explain these low respiratory quotients. In a single experiment Gréhant and Quinquaud also analyzed the gases of the venous blood, and found no excess of CO_2 in it. From this they draw the far-reaching conclusions that not only is the excretion of the CO_2 hindered, but also that a diminution in the oxidation processes of the organism is caused "*par l'intermé diaire du système nerveux et des lésions dyscrasiques secondaires*" in artificially-produced diseases of the lungs. Loewy, on the other hand, did not deduce a general lessening of the respiratory metabolism from this diminution of the respiratory quotient. He is rather of the opinion that the metabolism changes qualitatively, the molecular decompositions stopping short of the formation of their normal end-products. He supported this idea by successfully demonstrating an increase in the carbon excreted in the urine. But, unfortunately, he does not give the exact figures, and leaves it an open question whether the increase of carbon in the urine did actually cover the diminution of the CO_2 expired. In the same way Gréhant and Quinquaud's single gas estimation cannot be held to settle the question whether there is or is not a retention of CO_2 in the blood. Repetition of the experiments is all the more necessary because Kossel did find an accumulation of CO_2 in the blood of a cyanotic patient with lung disease. Krehl, like Loewy and Riethus, inclines to the belief that the diminution of the respiratory quotient in the infections may be due to changes in the metabolism. He adds the suggestion that the formation of antibodies may bear upon the point. It is, of course, obvious that the diminution is connected with the starvation or malnutrition of the animals or persons investigated. Kraus believes that this want of food alone is enough to explain it; but this is at least doubtful, because in Riethus' experiments the diminution was found so early that the influence of starvation could practically be excluded.

In certain cases Kraus found strikingly low values for the respiratory quotients of resting patients with well-compensated cardiac lesions. He correctly explained this as due to impediment in the excretion of CO_2, and not to changes in the metabolism; for his analyses of the gases in the venous blood showed an increase in the CO_2 present.

Summing up the foregoing results, it is evident that the respiratory

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quotient may be raised when the supply of O_2 is very deficient, and also that it may be lowered. This suggests that qualitative changes in the metabolism when O_2 is lacking are, at any rate, possible. Increase of the quotient above its normal value shows that intramolecular oxygen—that is to say, oxygen not derived directly from the respiration—is being consumed. Svenson has proved for the special condition of convalescence that oxygen may be set free by the conversion of sugar, which contains much of it, into fat which contains but little oxygen. Diminution of the quotient indicates either retention of CO_2 in the blood or the formation of intermediate decomposition products that are rich in oxygen, and may be excreted, for example, in the urine. As Magnus-Levy has briefly set out, it is probable that these processes concern only relatively small quantities of oxygen; yet they are not without their importance.

It seems an obvious step to confirm this qualitative alteration in the metabolism by the direct discovery of the intermediate products that point to the lessened intensity of the processes of oxidation. But it is necessary to lay stress upon the objections to any such interpretation of their discovery in large amount. Such a discovery would be far from proving that the body was insufficiently supplied with oxygen; it is much more probable that these intermediate products would result from an interruption of the activity of the cells due to disease. One would be justified in supposing, for example, that enough oxygen was present to complete the processes of oxidation, but that the tissues were no longer "bathed in oxygen," and were for that reason less active.

A whole series of chemical compounds has been described as the intermediate products of the metabolism in oxygen starvation. The older authors so describe oxalic acid, which was regarded by Frerichs and by Woehler (59) as a product of the incomplete oxidation of uric acid. Fürbringer (60), on the other hand, believes that the excretion of oxalic acid can be increased by either a rise or a fall in the oxidation. A number of authors have found a large amount of oxalic acid in the urine when the supply of O_2 was deficient; the more recent work of Ajello (61), of Reale and Boeri (62), and of Terray (63), may be mentioned here. Reale and Boeri experimented upon dogs, impeding their respiration by the use of a Sayre's plaster jacket. They came to the remarkable conclusion that the excretion of oxalic acid corresponded to the degree of dyspnœa produced, and that both the dyspnœa and the oxalic acid grew less in the course of a few days, apparently by the adaptation of the organism to the altered conditions of its life. But, holding in view Mohr and Salomon's (64) recent work upon the excretion of oxalic acid, it is as well to keep an open mind upon this subject. These authors found that the oxalic acid excreted in pneumonia was not appreciably increased, and that it had no connection with the formation or excretion of uric acid.

A certain importance has been attributed to uric acid in this connection. Bartels (65) taught that it is excreted in augmented quantity in dyspnœa because it is a product of incomplete combustion. We know now that uric acid is formed by the breaking down of nuclear substance; hence this view may be disregarded, excepting in so far as it

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may be taken to indicate the fact that the decomposition of cellular substance is increased in dyspnœa.

Clinical experience shows that in cases of uncompensated heart disease the excretion of uric acid is generally at the normal rate. Sometimes it is augmented (66-69); but, as the next chapter will clearly prove, this fact must not be understood to indicate that the production of uric acid is increased, for it is to be explained by the variations occurring in its excretion. Experimental results like those of Ajello, for example, who found such an increase in the uric acid output of a dyspnœic dog, can give rise to no more definite conclusion. A greater historical interest attaches to Simanowski and Schoumoff's application of Nencki's benzene method to animals with dyspnœa (70). Adding benzene to the food of a healthy animal, they measured the amount of it oxidized to phenol. They then impeded the animal's respiration, placing a ligature round the trachea, and found that the phenol in the urine fell to one-third of its former value. From this they deduced that the energy with which oxidation took place was lessened. But objections may properly be raised against this line of argument; it is not justifiable to assume that the absorption of the benzene and the excretion of the phenol remain unimpaired during dyspnœa, so that no particular importance can be given to these experiments.

Of greater significance is the fact that considerable quantities of lactic acid are found in the urine when the aëration of the blood is hindered; fermentable sugar may even be found if the supply of O_2 be very much curtailed. Such curtailment may be effected in animals in a variety of ways—by poisoning with CO, morphine, amyl nitrite, cocaine, veratrine, curare, or strychnine; by cooling; or by direct limitation of the supply of O_2. In the early days of physiology, sugar was found in the urine of dogs poisoned with CO by Richardson (71) and also by Senff (72); Senator (73) found it in the urine of dogs with dyspnœa; while Dastre (74) observed that the sugar in the blood was increased under similar circumstances. Hesse and Friedberg (75) proved that CO-poisoning in man was almost always accompanied by glycosuria. Finally, Hoppe-Seyler (76) and his pupils, Araki (77), Zillesen (78), and Irisawa (79), have studied the glycosuria that occurs under a great variety of conditions that have a single point in common—namely, a diminution in the supply of oxygen to the tissues.

Considering first the excretion of lactic acid, the question at once arises whether this really is a direct consequence of the lack of oxygen, or is rather determined by the simultaneous injury done to the functions of the liver. A number of observations argue in favour of the latter view. Lactic acid has always been found in the urine after extirpation of the liver; Minkowski (80) noted this in the goose, Nebelthau (81) in the frog, Salaskin and Zalesky (82) in dogs. The same thing is known to occur in grave disorders of the liver—in acute yellow atrophy of the liver, for example, and in phosphorus-poisoning. Particular reference may here be made to the work of Minkowski (83), who states that the urinary lactic acid found by Hoppe-Seyler and his pupils must originate in this way. In favour of the former view is the fact that Araki observed

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no impairment of the urea-forming activity of the liver, which was, on the contrary, increased in asphyxia; and in his experiments with Eck's fistulæ he never found lactic acid in the urine, but constantly noticed an increase in the excretion of ammonia. This makes it look as if the excretion of lactic acid was primarily determined by the want of oxygen, and the most recent writers on the question, Saito and Katsuyama (84), subscribe to this view. Experimenting on fowls, they invariably found a distinct increase in the lactic acid of the blood. Lactic acid has repeatedly been discovered in the blood of human beings during asphyxia. Münzer (85) and Palma observed it in persons poisoned by CO, while Voges and also Zülzer (86) found it in cases of grave heart disease. Irisawa found from 0·2 to 0·38 per cent. of lactic acid in the agonal urine of three patients; it was also present in greater amounts in the blood of persons who had died with embarrassed respiration than in others. Hoppe-Seyler (87) proved that the lactic acid of asphyxia was paralactic acid (= d-ethylidene-lactic acid).

The statements made about the glycosuria are less uniform. At any rate, it is clear that asphyxia does not cause sugar to appear in the urine of different kinds of animals with equal promptitude. Thus, Saito and Katsuyama found no glycosuria in fowls under these conditions, while Araki did find it, as did Weintraud (88) in ducks poisoned with coal-gas. It is very remarkable that Straub (89) should have found no glycosuria in starving animals that were asphyxiated; he employs the fact to explain Garofallo's (90) negative results. A similar variety is to be noted in the sources ascribed to the urinary sugar. Straub, working with CO-poisoned dogs, only observed glycosuria when the animals had a plentiful supply of protein to decompose. If the diet consisted mainly of carbohydrate (bread), the sugar vanished, and could not be made to reappear in the urine even by the direct addition of grape-sugar to the diet. Rosenstein (91) agrees with him; he observed that sugar in the diet did not augment the glycosuria, although feeding with the mother-liquor left after the crystallization of leucin from the fluid of a fibrin digestion did do so.

Münzer and Palma, on the other hand, found no difficulty in producing alimentary glycosuria in persons poisoned by CO. Straub's experiments led him to conclude that the sugar was derived from an increase in the decomposition of protein, although the nitrogen estimations did not indicate any such increase; his main point, however, is to dispute Araki's view that the excretion of sugar depends upon inadequate oxidation processes. He quotes one of Senff's experiments; Senff injected grape-sugar into the jugular veins of dogs fed upon meat, and found that when such animals were poisoned with CO they excreted practically no more sugar than did other animals injected with normal saline. But I cannot regard this experiment as conclusive, since my own experience is that the direct injection of sugar regularly produces glycosuria. And, further, a very important discovery of Araki's is in direct contradiction to Straub's view. Araki observed that if sodium lactate was injected subcutaneously into normal animals it was entirely oxidized into CO_2, whereas animals poisoned by CO excreted it almost all unchanged.

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Araki and Seegen (92) record that when lactic acid and sugar appear in the urine during asphyxia the glycogen contained in the liver grows less, a fact pointing in the same direction. Reference must also be made to another very interesting observation of Araki's—namely, that the synthesis of benzoic acid and glycocoll to form hippuric acid in the kidneys is prevented in asphyxia and CO-poisoning. And, finally, it may be mentioned that Lépine and Boulud (93) found substances they call leucomaines in the urine of asphyxia. These substances hindered the glycolysis of normal blood *in vitro*, and when injected into normal animals were able to produce glycosuria lasting a whole day. These authors also found this diabetogenic substance in the blood of a few pneumonia patients; it is a crystalloid, and occurs in the serum, not in the red cells. These results have not yet been confirmed.

Concerning other highly-oxidized compounds in the urine, see below under the heading The Commixture of the Nitrogenous Constituents.

It is clear, then, that the question of the intermediate products of the metabolism is far from being fully understood. Their origin still remains uncertain; although oxalic acid is probably derived mainly from protein, particularly gelatinous substances, it is quite doubtful whether lactic acid and sugar come from the protein. Hence one is justified in saying that *it is likely that sugar and lactic acid appear in the urine in consequence of a qualitative change in the metabolism due to lack of oxygen.*

E.—ON THE NITROGENOUS METABOLISM IN HEART AND LUNG DISEASE.

With the single exception of Möller's old experiments, which lasted for periods of five hours, the investigations made into the respiratory metabolism all employ the method of analyzing samples of gases taken from the lungs during fasting. They all yield figures indicating the decomposition of the tissues independently of the food absorbed. But, as is well known, investigations of the nitrogenous metabolism aim at getting out a balance-sheet for the nitrogen, establishing the relation between its intake and output, so that conclusions can be drawn as to the putting on of protein or the increased breaking down of the proteins of the body. Investigations like these are naturally very difficult to carry through at the bedside. For one thing, it is not easy to regularize the diet in severe illness; for another, the interpretation of the results obtained is difficult. In the infective disorders several disturbing influences are at work together—the infection, the fever, and the resulting lack of O_2; and when the fever has subsided there may be the absorption of inflammatory products to consider—that of a pneumonic lung, for example. And even in the non-infectious diseases, such as emphysema or compensated lesions of the heart, it is difficult to obtain exact results. In such cases the excretion of water, and with it the composition of the body fluids, is upset; œdema may appear, and may absorb a part of the nitrogenous decomposition products that should be excreted in the urine, so that it is no longer possible to compare the input and output of nitrogen for any given period.

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For these reasons there exist but few investigations bearing on these points, while some of them were directed towards the solution of other problems. Those dealing with the simplest of the relations under consideration shall be discussed first. Eichhorst's examinations of children with diphtheria are now only of historical interest; he found (94) that the urea was not increased, but the methods he employed were severely criticised later (Voit). Von Noorden (95) investigated the case of a patient who had severe dyspnœa due to syphilitic stenosis of the larynx, and his results are of importance on account of their completeness. The patient was in a fair state of nutrition, and was observed for three days. During this period she took only water, bouillon, and coffee, and so was practically fasting. The quantity of urine was normal, and it contained normal amounts of nitrogen—7·0, 5·7, and 6·1 grammes. It is a pity that this experiment could not be carried further. Figures for cardiac cases have been published by Schneider (96), Husche (68), and Kobler (69), and Husche worked out balance-sheets for the nitrogen. He found that in many cases where compensation failed for a short time, only small amounts of nitrogenous decomposition products were stored up, although much fluid was retained in the body. But in other cases, particularly those where the loss of compensation lasted longer, these products were largely retained, and when the amount of urine was increased by the exhibition of a diuretic, very considerable quantities of them were excreted. He found that under conditions such as these the output of nitrogen might overtop the input by from 30 to 40 grammes; as a rule, this extra excretion of stored-up nitrogenous bodies into the urine lasted for only a short time—a day or two. The rise and fall of the elimination of nitrogen usually ran nearly parallel with the rise and fall in the amount of urine passed, but not absolutely so; the accumulation and excretion of these urinary nitrogenous compounds frequently anticipated the corresponding diminution and increased excretion of the urine. Husche's determinations seem to prove that individual variations may occur; while it is chiefly water that accumulates in the transudates of acute cardiac failure, in certain cases a considerable retention of urinary compounds may occur. It is not possible to decide from Husche's or Schneider's figures whether the decomposition of protein was increased or diminished.

Turning next to pulmonary diseases, exact investigations of phthisical patients have been recorded by Goodbody (97), Bardswell and Chapman, and also by Mitulescu (98), Mircoli and Soleri (99), Klemperer (100), and, finally, by Blumenfeld (101). Yet it is impossible to deduce from these observations any definite inferences as to the impairment of the metabolism due to the want of oxygen.

Some of them were undertaken to test for the occurrence of toxines due to the decomposition of protein, others to investigate the use made of the food given, and others to study the action of food-cures. For present purposes it is of interest to note that they show that the nitrogenous metabolism of phthisical persons may be entirely normal, and that in other cases the decomposition of protein may be above the normal even when underfeeding can be excluded. Mircoli and Soleri, in par-

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ticular, found that even afebrile cases might fail to remain in metabolic equilibrium, unless the input of nitrogen and of calories were respectively 50 and 77 per cent. above the normal values found for healthy persons; the utilization of the food given to such cases remained unimpaired. For this reason these authors make mention of a formal nitrogen diabetes. Equilibrium was not established short of the daily supply of 28 grammes nitrogen, and of 50 calories per kilogramme.

It cannot be denied that these figures appear improbably large. But Mitulescu also has found a strikingly large protein decomposition in phthisis, and his simultaneous determination of the phosphorus balance-sheet makes it appear likely that the cells of the tissues are being melted down. Klemperer, too, as is well known, was inclined to explain the high figures for the nitrogen excretion of Cetti during his fast by the supposition that he was tuberculous. But everyday experience of feeding treatments proves that it is quite easy to make phthisical persons put on nitrogen. Goodbody is led to the not unnatural conclusion that this result is more readily obtained with ill-fed patients such as these than with healthy people, for the same thing is, of course, true of all ill-fed persons. To quote a case from the literature, von Noorden (102) found that during several days an afebrile case of phthisis put on small amounts of nitrogen on a diet containing 11·6 grammes nitrogen, and giving 46 calories per kilogramme. Blumenfeld, giving a patient about 19 grammes nitrogen and 956 calories a day, found that she put on an average of 1·7 grammes nitrogen. In tuberculosis, of course, the patients are likely to lose protein in their sputa, and also in consequence of their exhausting perspirations.

Lanz (103) analyzed the sputum in sixteen phthisical cases at various stages of their disease, and found the average losses of protein and nitrogen to be 4·13 grammes and 0·66 gramme per diem respectively. This corresponds to about 5 per cent. of the total nitrogenous output, estimated by Lanz at an average of 12 grammes a day. Summing up all these observations, one will not be far wrong in saying that the extent of the nitrogenous metabolism in afebrile phthisis depends chiefly upon the diet, but that in many cases it is abnormally large, though it can be made up by overfeeding. For the effect of fever here, see the chapter on Fever.

Turning next to pneumonia, there is an investigation of Moraczewsky's (104) based on the idea that there is a retention of water, and hence, by the theory of dilute solutions, that there must be an increased metabolism. But it is hardly possible to follow this author in his theoretical deductions. Leaving out of consideration the febrile period, it may be mentioned that Moraczewsky almost always observed an increased excretion of nitrogen after the crisis; this increase repeated itself a few days later, and after that the normal level was attained. This postcritical increase in the urinary nitrogen would depend partly upon the previous retention, and partly upon the absorption of the exudate. In lobar pneumonia this absorption takes place by autolysis, it may be noted, as the admirable work of Müller and Simon (105) proves. The

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autolysis mainly produces amino-acids, and, as Simon observes, these find their way into the urine in the physiological process of resolution.

We have seen that the investigations quoted above can teach us practically nothing about the effect on the nitrogenous decomposition exerted by the impaired respiration of cardiac and pulmonary disease. From this point of view the data of Oppenheim (106) are the only ones applicable to human beings. He found that muscular exertion, if pushed till extreme dyspnœa occurred, increased the protein decomposition that was normal for the diet being given; and that in Argutinsky's experiments work led to augmentation of the protein decomposed is a familiar fact. The differences between Pflüger's views and Voit's will not be discussed here; it suffices to say that Voit's supporters explain the increased breaking down of protein observed by Argutinsky in his experiments upon himself by his dyspnœa.

To settle the question whether it is the dyspnœa that increases the decomposition of protein experiments upon animals only are available at present. We find that a fairly considerable impediment to the respiration augments the nitrogen excretion but little [Senator]; but that if the impediment becomes great [A. Fränkel (107)], the augmentation may be considerable, and may last one or two days longer than the dyspnœa. This fact has been established in many ways and by many experimenters [R. Fleischer and Pentzoldt (108), Fränkel and Geppert (109), Klemperer (110) and Praussnitz (111); for CO-poisoning by Araki]. Colosanti (112) is the only observer who comes to the opposite conclusion, and his competence is such that his work cannot be passed by. Colosanti and Palamenti obstructed the breathing by chemical and by mechanical means, and found that the percentages of urea and nitrogen in the urine were both subnormal so long as the obstruction was maintained, rising again when the impediment was removed. They also expressly stated that the secretion of urine ceased during the dyspnœa. But one must hesitate before accepting unqualified their conclusion that the lessened supply of O_2 diminished the activity of the regressive metamorphoses of the organism.

The German authors quoted above found varying figures for the increase in the protein broken down. The daily average was 1 to 2 grammes; but the figures lack uniformity, and this is particularly the case with the nitrogen balance-sheets for the subsequent period. The highest values are those of Fränkel and Geppert, who found an increase of 2 to 3 grammes in fasting dogs; when the animals were given a mixed diet and came to be in nitrogen equilibrium, the increase fell to 1 gramme. Klemperer, too, succeeded in diminishing the excessive loss of nitrogen very considerably by feeding with moderate amounts of protein and an excess of non-nitrogenous food.

These investigations prove that the decomposition of protein is increased in dyspnœa. Fränkel believes that this is due solely to the molecular necrosis of the cells and the melting down of the tissues consequent on the lack of O_2; Klemperer, in view of the special effects of the dyspnœa produced by muscular exertion, attributes the increased protein decomposition rather to poison produced by the dyspnœa;

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Praussnitz has it that the primary effect of dyspnœa is to increase the breaking down of non-nitrogenous bodies, the augmented protein decomposition occurring secondarily. Which of these views is correct still remains an open question.

F.—THE INFLUENCE OF CARDIAC AND PULMONARY DISEASE UPON THE ORGANS OF DIGESTION.

Affections of the alimentary tract occurring during the course of disorders of the heart and lungs will be considered here as direct consequences of the primary lesion, and without regard to infective processes. For this reason the diseases of the heart and lungs may be treated of together, because pulmonary affections (such as emphysema or chronic bronchitis) lead to secondary failure of the heart. The influence of fever and of infection will be found in the chapter on Fever.

The nutrition may remain unimpaired if the lesion of the circulatory apparatus is well compensated. In other cases, however, and particularly if compensation fails, the patients experience discomfort whenever the stomach is full; more especially after taking flatulent food-stuffs they are liable to feelings of pressure and fullness, and if the congestion increases, their appetite is likely to fail. It is obvious that these discomforts are primarily due to hampering of the action of the diaphragm by the stomach, which is distended with either food or gas. It only happens occasionally and in the severest cases that starvation and its associated metabolic changes are thus induced. On the other hand, these patients often have good appetites, and take more food than is really required in view of the small amount of physical exertion they are put to. This sometimes occasions a considerable increase in their weight, particularly if they are confined to bed. The connection between these two circumstances was first pointed out by Oertel (113). There is no reason to doubt that these gastro-intestinal symptoms, when they do occur, are essentially caused by the congestion and hyperæmia of the mucous membrane. Whether actual catarrh is present in any given case is often hard to determine; at any rate, Krehl (114) quite rightly points out that cardiac cases show a great tendency to furring of the tongue and stomatitis, and often make their first appearance before the medical man on account of digestive disturbances. The tendency to constipation which they often exhibit is mainly due to their inability to get about.

The gastric secretions have been investigated in several instances and with various results. Summing up the work of Huster (115), Einhorn (116), Adler and Stern (117), Hautecœur (118), and Yorns (119), it may be said that when the cardiac lesion is compensated, the secretion of HCl is generally normal. But if there is a high degree of congestion, the secretion may wane considerably, or even dry up. Chelmonski (120) found the same state of things in emphysema with grave dyspnœa.

There are also a few experiments upon the absorption of food during venous congestion. Grassmann (121) and Müller (122) observed that

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proteids and carbohydrates were taken up normally, while the absorption of fats was more or less impaired—18 per cent. of the fat reappeared in the fæces on the average. The removal of ascites did not improve the absorption of fat, so Grassmann and Müller concluded that the phenomenon could not be accounted for simply by the congestion—that is to say, by the impediment to the flow of chyle into the veins. They believe that it depends upon morbid changes in the intestinal epithelium, arising spontaneously from the arterial anæmia caused by the congestion. But this impaired absorption of fat is by no means constantly exhibited in cases of grave congestion—Husche, for example, found the utilization of fat quite normal in his cases. As regards the putrefaction of protein in the intestine, Brieger (123) found no increase in the aromatic urinary compounds, particularly in the phenol and indican, of advanced cardiac cases. Von Noorden similarly observed normal values for the sulphuric acid esters in pulmonary emphysema and uncompensated cardiac disease.

It is well known that circulatory disturbances influence the liver very considerably. Heart disease is often first indicated by the symptoms of hepatic congestion—namely, feelings of pressure, fullness, and pain. But we do not know much about the upset of the hepatic functions. Patients with the signs of congestion are, of course, frequently of a dirty-yellowish tint, or even definitely jaundiced, and the fæces are hardly ever free from bile-pigment; but the clinical picture is often obscured by the spontaneous appearance of disease in the liver or the bile-ducts. In these cases there is always a depositing of bilirubin. The jaundice is generally slight, and the corresponding concentration of the bile in the blood is rarely sufficient to occasion the appearance of that pigment in the urine. There is often a considerable quantity of hydrobilirubin in the urine of persons who show the signs of congestion of the liver, and this condition used to be erroneously described as hydrobilirubin jaundice, and not as a true jaundice. This idea must now be given up, seeing that the hydrobilirubin is known to be absorbed from the intestine. A variety of causes might be supposed to underlie the jaundice associated with circulatory disturbances. Firstly, catarrh of the small intestine, or of the bile-passages, might cause the jaundice. In the second place, it is possible that the bile is secreted in abnormal directions, producing Minkowski's acachectic icterus. Thirdly, the marked hydrobilirubinuria suggests that lesions of the circulatory system tend to the production of an excess of pigment in the bile; and there are other observations that support this idea. Grawitz (124) remarked that the hæmoglobin is abnormally loosely attached to the corpuscular stroma when compensation has failed, and concludes that the resisting power of the red cells is lessened under these circumstances. Ottolenghi (125) measured their resisting power in asphyxia by Mosso's method, and found that it was lessened. He also found that asphyxial blood gives up its pigment with abnormal rapidity, using Bizzozero's lithometer. Thus the conclusion is that an abnormally large amount of hæmoglobin is converted into bilirubin during venous congestion. Grawitz explains the facts thus: A true hæmoglobinæmia could not be found in his patients; hence it is to be assumed that the resistance of the red corpuscles was lowered,

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and that more of them were broken up in the liver. This would account for the production of an excess of bile-pigment, and for the secretion of bile which is sticky and contains an excess of colouring matter. Some of this bile would be reabsorbed, occasioning a slight jaundice; the greater part of it would enter the intestine, and give rise to the increase of the hydrobilirubin in the fæces and urine.

In conclusion, it may be noted that Ajello (126) found that the toxicity of the bile of asphyxiated animals was increased by one-sixth.

G.—THE BLOOD IN DISEASES OF THE HEART AND LUNGS.

The occurrence of dropsy in these diseases has naturally directed the attention of medical men to the behaviour of the blood, and particularly to its percentage of water. These points have been investigated repeatedly, but the results obtained are often contradictory, and even now cannot all be included in a single explanation. This is due, I believe, to the lack of the necessary experimental groundwork. It is certain that water is retained in the body when dropsy occurs; but the intake and output of water under these conditions has never been exactly investigated. The secretion of urine has often been examined. It has always been noted that the dyspnœa must increase the amount of water exhaled from the lungs, and there can be no doubt but that it does so now that the occurrence of exaggerated respiration is established. And, finally, Peiper (127) and Jansen (128) have demonstrated that water is given off at an increased rate from the skin overlying œdematous tissues. But how far the skin and lungs can thus make up for the diminished activity of the kidneys is not known. The concomitant variations in the weight of the body can give a rough idea of what is going on, but a more delicate analysis is wholly lacking.

While this work is passing through the press, the method by which the question must be attacked has been worked out, mainly in Rubner's laboratory. Schwenkenbecher (154) and Lany (155) have just adapted it to the investigation of disease.

There is one point that goes far to explain the differences in the experimental results, and that is the variety of the methods employed, particularly as regards the way in which the blood is drawn. In most cases the so-called capillary blood is used—that is to say, blood drawn by puncture of the ear or the finger-tip. But it is obviously uncertain from what sort of vessels such blood actually comes. Piotrowski (129) found that such blood was practically identical with venous blood. Oertel (130) and Grawitz were rather led to the opposite conclusion. But it is quite certain that what is wanted is *the comparative examination of arterial and venous blood.* The very recent work of O. Hess (131) proves the point. Hess, working on healthy animals, observed that when the blood-pressure was artificially varied, the arterial blood steadily maintained its composition unchanged; the venous blood, on the other hand, became more concentrated when the pressure rose, more dilute (as much as 25 per cent.) when it fell. He believes that the composition of the

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venous blood returns to the normal mainly in the lungs; when it is diluted it parts with fluid in the lungs only, and when it has become concentrated—in consequence of a rise in the blood-pressure—it takes up fluid again in the lungs and also in the liver. Thus, Hess believes that the lungs, and to a less extent the liver also, are able to regulate the percentage of fluid in the blood, and to keep that of the arterial blood constant.

These conclusions have been attacked by Bönniger (132) on the score of mechanical considerations. Piotrowski, too, did not succeed in altering the concentration of the venous blood in animals by raising their blood-pressure. But Grawitz has confirmed Hess's results. He partially cut off the supply of arterial blood to a certain vascular area, and thus lowered the blood-pressure, and then found that the blood in the corresponding capillaries and veins became more watery. Grawitz holds that this was undoubtedly due to the absorption of fluid from the tissues. The valuable observations of Piotrowski confirm this. Piotrowski set cardiac patients to work until a fall in their blood-pressure occurred, and noted a diminution in the number of their blood cells; but muscular work was found to increase the blood-pressure of cardiac patients whose compensation was better, and the venous blood of such persons was then found to contain an increased number (perhaps 20 per cent. more) of red corpuscles. Hence one is justified in concluding that the blood-pressure does influence the specific gravity of the venous blood, and that the latter may become diluted by the absorption of fluid from the tissues. Stress must also be laid on the fact that such dilution also occurs when the blood-pressure of the healthy changes, or when healthy animals are bled.

After these preliminary remarks we may consider the phenomena observed in congestion. Only the so-called capillary or venous blood is concerned.

Grawitz (124) and Askanazy (134) have recently summed the matter up. It appears that (1) when the compensation is good, the composition of the blood remains normal; (2) when compensation fails, and particularly in the early stages of its failure, the blood becomes more dilute; it may either remain dilute, or return to the normal, or even become abnormally concentrated, as the case progresses. The last-mentioned condition is often found in severe cases of prolonged heart failure. The number of red corpuscles in the diluted blood is lessened; in the concentrated blood it is generally found to be increased.[1] Things are found to be otherwise, however, if the water contained in the serum is examined as well as the blood as a whole; the serum is invariably dilute, and usually is the more so the higher the degree of the œdema. No correspondence has been found to exist between the figures for the blood and those yielded by the serum.

How are these results to be interpreted? The simplest case is that in which both the serum and the whole blood are found to be dilute.

[1] This has been worked out in various ways: by blood-counts, determinations of the hæmoglobin or the dried residue [Stintzing and Gumprecht (135)], or the specific gravity [Hammerschlag (136)]. They are not all free from objection, but the conclusions to which they lead may be regarded as certain.

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Grawitz is inclined to attribute this to the fall in the blood-pressure, which, as we have seen, causes fluid to be absorbed from the tissues and produces the dilution. He says that in failing compensation such as this the dilution of the blood first begins in the capillaries, and is most marked in the veins, and believes that its inception cannot be attributed to the retention of water that follows the diminished activity of the kidneys. The lessening of the secretion of urine is similarly caused by the diminution in the arterial blood-pressure, and it runs parallel with the dilution of the blood in the capillaries. This view can, of course, be opposed on the strength of the observations recorded above; but it is not possible to decide whether it is a retention of fluid or the circulation through the tissues that primarily causes the dilution. I believe that the question could only be settled by comparative estimations of the amount of fluid in the organs and in the blood of animals; only small differences are to be looked for, although the organs must naturally lose fluid if they pass it on into the blood. And, further, it is questionable whether any great dilution of the serum can be effected by the addition of lymph to it. Lymph is certainly more watery than serum, but its dried residue amounts to as much as two-thirds of that of the latter. Grawitz's view is hardly wide enough, and it seems better to suppose that in the first place œdema of the blood occurs in consequence of the diminished excretion of urine. This retention of fluid dilutes the blood, which may be still further diluted by lymph passed on to it by the tissues so long as they preserve their elastic tension, if the blood-pressure falls. In any case the volume of the blood increases, and occasions the *volumen auctum* of Stintzing and Gumprecht, or the *plethora serosa* of Oertel. Krehl, too, believes that this is the true state of affairs. But one cannot be absolutely certain that it is so, because methods for determining the exact volume of the blood are as yet not fully worked out.

Various authors have also suggested that the serum might become diluted by the loss of its protein constituents, the loss being due partly to the chronic malnutrition and partly to the albuminuria. In that case the increase in the fluids of the serum would not be a true plethora at all. But this view is contradicted by the fact that the blood of Stintzing and Gumprecht's patients, though found to be dilute while cardiac compensation failed, was repeatedly observed to return to the normal density again when compensation was once more established. This fact also negatives the idea, mentioned above, that the number of red cells sank because a quantity of them were destroyed.

A certain amount of light, then, has been thrown upon the factors determining dilution of the blood. But it is very hard to explain the cases where the specific gravity of the blood is increased, the red cells being more numerous and the serum more watery than is normal. We may first observe that Grawitz found that the concentration of the blood in the capillaries was greater than that of the blood in the veins; while Askanazy, puncturing the heart immediately after death, proved that blood drawn from the right side of the heart was not more watery than venous blood. Oertel had concluded, however, that the blood from the heart was the more watery of the two, owing to its dilution with the

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lymph streaming in through the thoracic duct. But, thanks to Askanazy's observations, this idea can now be given up. It accords better with the present state of our knowledge to assume that the stream of lymph leaving the thoracic duct is far from being augmented in congestion; it is much more likely that the high pressure in the veins holds back the lymph, and that the observed dilatation of the thoracic duct is a consequence of the lymph stasis thus produced.

Grawitz is of the opinion that the inspissation of the blood is chiefly due to the increase in the water given off from the lungs. In opposition to the older view of Oertel, he holds that the blood in the arteries is denser, becoming more dilute in the capillaries, under certain conditions, by processes of diffusion. A piece of work done by Schneider (137), under F. Müller's direction, has frequently been quoted in support of Grawitz's opinion. Schneider found that in most cases of mitral disease the count of the red corpuscles was increased, but that it was normal or subnormal in aortic incompetence; the contrast was explained by the assumption that the amount of water expired from the lungs was increased in mitral lesions. But he paid no attention to the concentration of the serum in his experiments. Hess has also interpreted the relations observed in uncompensated heart disease by the light of his views (given above) on the action of the lungs as regulators of the amount of fluid in the blood. He noted that blood which had become diluted by taking up lymph from the tissues parted with a large amount of plasma when the blood-pressure fell and it passed through the lungs. He therefore concluded that this regulating mechanism might also come into action when the heart was diseased, and might inspissate the blood before it went on into the greater circulation. The blood would be of abnormally large volume, but according to his view it would not have been diluted.

My own opinion is that Grawitz's view cannot be maintained. In the first place, we have no definite knowledge of the quantity of water given off in the lungs. Even if it be granted that this quantity is probably increased in dyspnœa, the fact that the concentrated blood yields an abnormally watery serum speaks emphatically against Grawitz's view that the increased excretion of water by the lungs is the only cause of the concentration of the blood. If Grawitz were right, the serum, as well as the blood, would leave an increased residue on drying. Thus the inspissation of the blood can only be explained by a diminution in the plasma it contains, such as might be occasioned by a change in the proportions of the plasma and the red cells. The well-known experiments of Cohnstein and Zuntz (138) have been brought forward repeatedly in support of this view. These authors observed that when the smaller vessels dilated, a number of them which had previously given passage to serum only began to contain red cells also. The red cells thus left the larger vessels to pass through the smaller ones, whereas during vaso-constriction they were rather confined to the larger vessels. These observations would also explain how Grawitz came to find the blood in the capillaries more concentrated than that in the veins; one would only have to make the additional hypothesis that the capillaries and

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the origins of the smaller venules are dilated in congestion, and Grawitz has not directly proved that this is the case. Askanazy's theory, that perhaps the vessels are rendered more permeable for plasma by the passage of CO_2-laden blood, can also be applied to the explanation of the concentration of the blood. It seems to me that if one presupposes a primary œdema of the blood, osmotic force would account for the withdrawal of fluid from it; at a later stage the elastic tension of the tissues would be much diminished by the establishment of œdema, and fluid would continue to pass out into the tissues after osmotic equilibrium had been attained, attracted by their loss of tone. In conclusion, the theory that a new formation of red cells takes place may be mentioned, for it has the support of most of the recent writers. The arguments for and against it will be detailed in the chapter on the Air at High Altitudes; only the chief objection to it will be noted here, and that is the fact that immature forms of red cells are not found.

So it appears that even nowadays there is but little certain knowledge of the *watery content* of the blood. For want of comparative investigations of both venous and arterial blood one has to fall back on hypothesis. The conclusions that have been drawn are not compatible with one another; great care should be exercised in the adoption of therapeutic measures based upon such conclusions.

So much, then, for the water in the blood. Its degree of *alkalinity* in congestion has also been determined; by the older authorities—von Jaksch (139), Peiper (140), Renzi (141), and Lépine (142)—with discordant results. In some cases an increase was observed, in others a decrease, and the methods employed were not uniform. Araki's are the only valuable results; he poisoned animals with CO, or gave them an atmosphere poor in O_2 to breathe, and found that the alkalinity of their blood was lessened by the appearance of lactic acid in it. Fodera and Rayona (143) partially confirmed these experiments, observing that the alkalinity of the blood was diminished during prolonged asphyxia. This was not the case, however, with speedy suffocation, a fact which indicates that it is the lactic acid which neutralizes the alkali in the blood.

The clinical work done upon the blood of patients by the newer methods of determining its alkalinity [Brandenburg, Gawronski] do not deal specially with cardiac or afebrile pulmonary disease.

Finally, it may be mentioned that von Jaksch found small quantities of uric acid in the blood during venous congestion.

Ferrai (145) has published the only experiments upon the *viscosity* of the blood. He states that saturation with CO_2 increases the viscosity of blood, but not that of serum. Perhaps light is thrown upon his observations by von Limbeck's discovery that exposure to CO_2 makes the red corpuscles swell. It may be remarked that Kraus could not fully confirm von Limbeck, who also attributed the lessening of the volume of the serum and its increase in density to the swelling of the red cells. Kraus found that the freezing-point of the serum was lowered almost imperceptibly, and that the diminution in its volume fell within the limits of the experimental error.

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The observation of Fano and Botazzi (146) may be added here. They remark that asphyxia augments the lowering of the *freezing-point* of serum. In the normal dog $\Delta = 0{\cdot}61 - 0{\cdot}62°$, in asphyxial blood $\Delta = 0{\cdot}63 - 0{\cdot}645°$.

The Italian literature contains some references to the *toxicity* of the blood, which would appear to be rendered poisonous by leucomaines in asphyxiated animals [Ottolenghi (147)].

The diminished resistance of the red cells is dealt with on p. 333.

The fact that the *total count and the differential count of the leucocytes* remain normal in heart disease has been already stated. Helber (148) finds that the same is true of the *blood-platelets*.

With regard to the *bile pigments*, bilirubin has frequently been found in connection with the slight jaundice seen in morbus cordis. Hydrobilirubin rapidly appears in the urine, and has been found in the serous fluids taken from the patients during life or after death; its detection in the patient's blood offers great technical difficulties, but has undoubtedly been effected *intra vitam* in one instance by Gerhardt (148). The blood of pulmonary cases has been examined again and again. The observations made in the febrile diseases—pneumonia, phthisis, etc.—will not be discussed here. The phenomena due to congestion in emphysema are identical with those seen in heart disease. In asthma a number of observers have recorded the appearance of many eosinophile cells in the blood [F. Fink (150), Gabrischewski (151)]; they may amount to 14·67 per cent. of the leucocytes. According to von Noorden (152) and Swerschewski (153) they are increased only at the onset of the attack.

H.—THE URINE IN DISEASES OF THE HEART AND LUNGS.

1. Its Quantity and Density.

The quantity and specific gravity of the urine are known to depend upon the amount of insensible perspiration as well as upon that of the fluid taken. Hence it is clear that simple obstruction of the breathing may concentrate the urine while an ample supply of water is being consumed; such obstruction increases the activity of the lungs and the evaporation of water from them, and also augments the amount given off from the skin, both reflexly and as a consequence of the unusual respiratory exertions made. There do not exist any exact measurements of the quantities involved here. It looks as if the increased activity of the lungs (or hyperventilation) was not of serious importance. At any rate, von Noorden, in commenting upon the experiments of Fränkel and Geppert, remarks that the diuresis regularly observed upon the days during which the dogs breathed in a diluted atmosphere was perhaps due to the increased work done by their hearts.

From a clinical point of view the chief interest lies in failure of the compensation. Here both heart and lungs are hampered, and the urine possesses the familiar characteristics of small quantity, high specific

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gravity, and marked concentration. Even if large amounts of fluid are imbibed they fail to produce their normal effect upon the secretion of the urine, and it is hardly increased. This is, no doubt, due to impairment of the renal circulation. It is to be regretted that nobody has hitherto adequately examined how far the evaporation from the skin and lungs makes up for this deficiency. The work done by Schwenkenbecher (154) and Lang (155) at any rate indicates how the problem should be attacked clinically. But at the present time we cannot do more than refer to Peiper and Jansen's observations, in which they noted an increase in the water evaporating from œdematous skin. The absolute values are not known, but it is certain that the compensation is incomplete, because œdema does appear.

It is a familiar fact that Oertel has proved that limitation of the consumption of water may increase the output of urine in dropsy. This occurs in only a certain number of the cases, and is naturally due to a diminution in the work demanded of the heart. Still, we know that valuable conclusions as to the activity of the heart or the reabsorption of exudates and transudates can be deduced from observations of the quantity of urine passed.

2. The Commixture of its Nitrogenous Constituents.

The output of nitrogen as a measure of the protein decomposition has been discussed already, and the difficulties attending both the working out of the nitrogenous balance-sheet and its interpretation have been indicated. It is easier to make out the mutual relations of the different nitrogenous compounds that are found in the urine; more attention has been directed to this point during recent years because of the improved chemical technique applied by Schöndorf to the estimation of urea, and by M. Pfaundler, M. Krüger, and Schmid, to the isolation of the monamino-acids.

The older investigations are but rarely serviceable; for one reason, no attention was paid to the alimentation of the patients, and for another, no sufficiently accurate method of estimating urea had then been worked out. In fact, all of them may be neglected excepting those in which the food taken was measured, the total nitrogen was estimated by Kjeldahl's method, and the uric acid was properly determined.

The more recent investigators mentioned all measured—

(*a*) The total nitrogen.

(*b*) The nitrogen in the precipitate given with phosphotungstic acid, which contains the ammonia, extractives, and purin bodies.

(*c*) The nitrogen in the filtrate of the above precipitate.

(*d*) The urea.

Subtracting (*c*) and (*d*) from (*a*), the result is taken to roughly represent the so-called amido-acids; some of these, such as the oxyproteinic acids, are rich in oxygen. This method has been employed by Landau (156), Ascoli and F. de Grazia (157), von Jaksch (158) and Halpern (159), in cases of disease of the heart or lungs. In tuberculosis the percentage of

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nitrogen passed as urea and as the other urinary constituents was normal, though the values for urea tended to be rather low, and those for the ammonia, purin bodies, and extractives rather high; the nitrogen as amido-acids was 2 per cent., the normal amount. A case of emphysema with *morbus cordis*, and a cardiac case with failure of the compensation, have been examined by von Jaksch. In the latter, 96 per cent. of the nitrogen was excreted as urea, and 4·8 per cent. appeared in the precipitate thrown down by phosphotungstic acid + HCl—here partly in the form of albumin. With the emphysematous patient 89·8 per cent. of the nitrogen was in the urea, 5·6 per cent. in the precipitate, and 1·0 per cent. was in the form of amino-acids. Von Jaksch also investigated a patient with pneumonia, but as the urine also contained sugar the results will not be quoted. The values found before and after fermentation, however, were not identical. No other determinations have been made in this manner so far.

Certain of the older experiments remain to be mentioned. Thus, Mircoli and Soleri employed Gumlich's modification of the Pflüger-Bleibtreu method, and in the early progressive stages of uncomplicated tuberculosis found low values—as low as 65 per cent.—for the nitrogen as urea. In cases where there was a tendency to pulmonary cicatrization the mean figures lay higher, up to 84 per cent.; the same was true in phthisical patients with fever or with mixed infections. These authors quote some figures from the French scientists Berlioz (160) and Charrin, who found low percentages for the nitrogen as urea, or, as they prefer to put it, for the coefficient of oxidation. The German writers Halpern and von Jaksch, on the other hand, found the normal values given above when the diet was mixed.

It is still incumbent on us to quote some determinations that are even earlier in date, dealing with the uric acid, made by Voges, and repeated later by F. Friedrichsen. The latter determined the total nitrogen, the nitrogen excreted as NH_3, the nitrogen of the urea, and the nitrogen in the phosphotungstic acid precipitate, and at the same time recalculated Voges' analyses, correcting a few errors in them. In this way he arrived at figures showing that in severe circulatory stasis the excretion of uric acid remains at almost the normal level until death occurs; while others of the figures indicated that the uric acid continued to be excreted in normal amount, when the total nitrogenous excretion lessened and proved that retention was going on to a considerable extent. Under these circumstances the proportion of the total nitrogen to the nitrogen as uric acid naturally diminished. The most marked case of this occurred when the nitrogen as uric acid rose to 9·9 per cent. of the total nitrogen. Husche took up this line of work once again, using the same method. He observed that while some cardiac patients did excrete large quantities of uric acid at times, this excretion was not independent of the quantity of urine passed; but that the total nitrogen eliminated, the uric acid, and the diuresis did not always run parallel. Now, von Jaksch (13) had found that there is an increased amount of uric acid in the blood of persons in a state of dyspnœa. For this reason Husche concludes that the uric acid accumulates in the system during failure of compensation,

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and is washed out of it again when compensation is established once more, for he only found high values for the acid during marked diuresis. Yet it must be noted that if the percentages of the uric acid are recalculated and expressed in absolute weights, normal values result, excepting when there is a diuresis. Hence it is certain that uric acid, considered as an intermediate product of metabolism, is not formed in augmented amount (see p. 326).

Stanley Parkinson (*Practitioner*, 1906) examined a large number of tuberculous patients, and found the purin excretion increased 50 per cent. He concludes that the tissue metabolism is increased in tuberculosis.

In some of Friedrichsen's, Voges', and Husche's analyses the so-called residual nitrogen was very large in amount, both absolutely (28·3 grammes) and relatively (22·7 per cent.). Husche explains this by the preceding stasis. No such increase is found by von Jaksch during venous congestion, as the more recent analyses quoted above prove. In the first edition of the present work, von Noorden expressed the view that possibly uric acid, whether given in the food, subcutaneously injected, or reabsorbed from an exudate back into the blood-stream, might be oxidized into urea. This supposition would explain the lack of parallelism between the total nitrogen excretion and the excretion of uric acid, and may very well be correct.

A word must be added about the NH_3 excretion. It varies from 0·3 to 0·8 gramme, or practically within the normal limits. It reaches a maximum when the flow of urine is increased, and there may be some inconsiderable increase in its formation, as in the formation of uric acid, under these circumstances.

Concerning creatinin, we have only the old experiments of Hofmann (161) to draw upon. It is excreted in normal amount so long as compensation holds good, and after protracted failure of compensation the creatinin diminishes, probably because the nutrition also fails.

3. Albuminuria.

This is a matter of importance. The albuminuria of venous congestion is a familiar feature in cardiac insufficiency. Schreiber (162) first demonstrated that forcible compression of the thorax is enough to produce albuminuria. A number of experiments upon animals show that the same condition results from asphyxia, whether produced by stenosis of the trachea [Overbeck (163)], or by the inhalation of CO (Araki) or of an atmosphere poor in O_2. The researches of Schreiber's pupils, particularly Seelig (164), have thrown light upon albuminuria due to compression by showing that it may be regarded as a consequence of the fall in the blood-pressure caused by compressing the thorax. As it is only a transient albuminuria, there can be no ground for believing that any poison is formed to damage the renal cells. It may be added that Schreiber was most successful in producing albuminuria by strapping the chest in the case of half-grown persons. This corresponds with my

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own observation that young patients exhibiting spontaneous albuminuria mostly tend to a subnormal blood-pressure.

Where a general upset of the circulatory equilibrium is in question—in *morbus cordis*, for example—von Noorden has pointed out that the upset must be very considerable before albuminuria occurs. It seems that the renal epithelium learns to adapt itself to the altered circulation, and for a long time gives no passage to albumin. In simple venous congestion, where there is no inflammation and no renal degeneration, but little albumin gets through—rarely more than 1 or 2 grammes a day. Isolated samples of the urine, however, may contain 0·5 per cent., or even more, of albumin, particularly when the total volume of urine passed is small. The albumin usually disappears promptly when the congestion is relieved. From the older researches [von Noorden, Czatary (165)] it seems likely that relatively more serum-globulin than serum-albumin is excreted during venous congestion. More recently Cloetta (166) has stated that the amount of globulin was increased in heart failure, but that it diminished after a short treatment with digitalis.

It still remains to say that the albuminuria of the infective processes, such as phthisis and pneumonia, is partly due to the fever, and partly to the action of toxines. Thus Asch (167) succeeded in showing that the injection of sterile bacterial poisons into the arteries could produce severe inflammation and degeneration of the kidneys. Only Zvia (168) has endeavoured to refer the albuminuria due to congestion to protoplasmic poisons.

For information about the albumosuria of infectious pulmonary disease, see the chapter on Fever.

4. The Salts in the Urine.

Little is known about the salts excreted by the urine in diseases of the heart and lungs. In the non-infectious disorders there are no trustworthy experiments. In phthisis we have to thank A. Ott (169) for a number of balance-sheets of the mineral metabolism; they show that the demineralization so often discussed in the French literature does not usually occur in phthisis—at any rate, if a proper quantity of food is taken. The phenomenon may be seen in advanced cases, according to Ott, but it cannot be regarded either as a constant or as an early sign of phthisis.

The well-known retention of chlorine that occurs in pneumonia may be mentioned, so may Gourand's (170) observation that during the fever of pneumonia there is diminished excretion of phosphoric acid, chiefly affecting the earthy phosphates. He proposes to employ this fact for the differential diagnosis of tuberculosis, where the excretion of the earthy phosphates is augmented, a proposition standing in much need of support.

Concerning bilirubin and hydrobilirubin, see p. 333. See p. 325 for lactic acid, glucose, and oxalic acid.

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5. The Toxines in the Urine.

References to the urotoxic coefficient are to be found in the French literature. Duchamp (171) and Huchard (172) believe that it falls to half its value in failure of the compensation, being increased in pure cardiac hypertrophy. One knows that investigations carried out by Bouchard's method have hitherto been regarded with a very critical eye in Germany; the same may be said for Griffith's (173) isolation of a leucomaine crystallizing in white needles from the urine of cases of pneumonia.

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CHAPTER VII

DISEASES OF THE BLOOD

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Translated by J. A. Milroy, M.A., M.D.

I.—THE INFLUENCE OF DISEASES OF THE BLOOD ON OXIDATION PROCESSES.

The results of investigations into respiratory metabolism are of primary importance for the consideration of the processes of oxidation in the organism.

Experiments carried out on the dog by Bauer (1) have proved that the withdrawal of a considerable quantity of blood, amounting to 20 to 28 per cent. of the calculated total, does not usually exercise any important influence upon the quantity of oxygen consumed by the animal within the hours immediately following the blood-letting. A moderate diminution in gaseous exchange could be demonstrated only on the day subsequent to the operation, and this decrease affected the absorption of oxygen at an earlier date and to a more marked degree than the excretion of carbon dioxide. Finkler (2) found that rabbits showed an unaltered O_2 absorption and CO_2 excretion under similar conditions, even when the blood withdrawal amounted to one-third of the total amount. Lukjanow (3) found that an increase in the consumption of O_2 of somewhat more than 10 per cent. occurred immediately subsequent to the withdrawal of blood from rats and dogs. On the following day the values had again become normal. Frédéricq (4) observed, with the aid of his oxygenograph, that an average decrease in the consumption of oxygen of about 10 per cent. took place in the case of rabbits from which blood had been withdrawn during active digestion. Yet this decrease is absent in some cases. In one case there was actually noted a by no means inconsiderable increase. On the other hand, a temporary diminution in the consumption of O_2 occasionally occurs directly subsequent to the blood-letting in the case of fasting animals. Yet it must be admitted that the series of numbers given by Frédéricq vary in no small degree. Gürber (5) found that considerable losses of blood produced no permanent effect on respiratory metabolism in the case of rabbits, from which he had withdrawn so large a proportion of their blood that the number of red corpuscles fell to half the normal value, and in which the blood withdrawn had been replaced by an equal volume of an alkaline solution of cane-sugar containing sodium

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chloride. The same result also followed after blood-letting without subsequent replacement of the blood withdrawn. Gürber's experiments have a special claim for remark, since he repeated his experiments at first daily, later at greater intervals, until the composition of the blood had again become normal. It is thus evident that a marked effect upon gaseous exchange cannot be attained in experiments on animals by means of the artificial withdrawal of blood.

In 1869 Pettenkofer and Voit (6) carried out experiments on man which have a direct bearing on this question. They investigated the intake of a resting patient suffering from severe leuchæmia, and found the gaseous exchange in this case almost identical with that of healthy individuals taking the same diet. Magnus-Levy (7), however, interprets the foregoing results to mean that a more intense gaseous exchange occurred in the case of the patient suffering from leuchæmia than in the normal individual selected for comparison, because the former weighed 59·5 kilogrammes, while the latter had a weight of 70 kilogrammes. At an earlier date Hannover (8) had investigated the CO_2 excretion in four chlorotic girls, and obtained fairly normal values.

In two cases of pronounced chlorosis Kraus, using Zuntz and Geppert's method, found values for the O_2 intake and CO_2 output per minute and per kilogramme of body-weight amounting to 5·11 : 3·70 and 5·48 : 4·00 respectively.[1]

In a case of severe secondary traumatic anæmia the corresponding values were 4·58 : 3·45, and in a case of progressive pernicious anæmia 4·53 : 3·22. In four cases of severe anæmia associated with carcinoma of the stomach the values obtained varied between 4·12 : 2·75 and 5·94 : 4·06, and in four cases of leuchæmia the corresponding limits of variation were 3·47 : 4·42 and 4·63 : 5·34. According to Kraus, these values do not essentially exceed the normal physiological amounts in any direction, yet the quantities found nearly attain the upper physiological limit. The lower normal limiting values are never actually reached in any single case. Kraus concluded that the gaseous exchange during rest is not diminished, when it is compared with the normal condition, even in cases of severe anæmia. He was also able to show that the consumption of food influences the gaseous exchange in the same sense as in healthy individuals, and even to a numerically comparable extent. By increasing the amount of work done, Kraus was able to attain a well-marked rise in the respiratory interchange of his patient, although this increase did not reach the amount which, *ceteris paribus*, one finds in the healthy subject.

In addition to Kraus and Chvostek, Bohland (11) and Meyer (12) investigated with the aid of the same method the respiratory gaseous exchange in different cases of leuchæmia, chlorosis, and the anæmia of anchylostomiasis. They found that the O_2 consumed by their patients varied from 4·3 to 6·8, while the CO_2 output varied between 3·3 and 5·8. Meyer states that in one case of leuchæmia the consumption of O_2 amounted to 7·9. These are values which considerably exceed the normal figures for the resting organism, which amount on the average

[1] The number placed before the double point corresponds to the quantity of oxygen consumed, while that placed after it expresses the quantity of carbon dioxide excreted.

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to 3·08 : 3·81. On this account they give rise to the question as to whether the reasons for the increase in gaseous exchange observed by Bohland and Meyer are dependent upon the nature of the disease in itself, or are due to certain peculiarities in the experimental conditions. A statement made by Bohland appears to be of value in this connection. He mentions that some of his experiments were carried out on fasting patients, some three to four hours after breakfast, and others five or six hours after the midday meal—*i.e.*, at a period during which the patients were still under the influence of digestion. Meyer makes no special statements with regard to this point. Magnus-Levy (7) carried out seven experiments on a fasting woman suffering from pseudo-leuchæmia. He found a gradual diminution from initial high values to such as still somewhat exceeded the normal value even at the conclusion of the experiments. The higher values determined by him amounted to 6·1 : 4·58 and 6·1 : 4·18 respectively, while the lowest values obtained were 4·32 : 3·17 and 4·43 : 3·38 respectively. An investigation undertaken by him on a patient suffering from severe anæmia following abortion yielded a value of 4·26 : 3·6 at the height of the illness, while a value of 3·83 : 3·35 was found at the time of improvement.

In Thiele and Nehring's cases the values for the fasting condition varied in the cases of chlorosis from 3·44 : 3·10 to 3·51 : 3·01 in Case I., from 3·00 : 2·77 to 3·30 : 2·57 in Case II., and the fasting value amounted in Case III, to 3·38 : 3·29. The values in the fasting state amounted to 4·05 : 3·44 and 4·26 : 3·68 in a case of secondary anæmia, and in a case of pernicious anæmia they varied from 3·86 : 2·8 to 4·38 : 3·03. It follows that fairly normal conditions were present in the cases of chlorosis, while a certain rise of the respiratory gaseous interchange was observable in the case of secondary anæmia. Further, Henius (15) recently established a similar result for chlorosis by finding a value of 4·3 : 3·1. Magnus-Levy (14) determined a value of 5·18 : 4·05 in a case of chronic leuchæmia.

If special notice be taken of these values which have been determined for the fasting state, a comprehensive consideration of the foregoing values seems to justify the conclusion that a diminution of the gaseous interchange during respiration scarcely ever occurs in diseases of the blood. On the contrary, an increase of the respiratory interchange can occasionally be observed. In this regard the following quotation of von Noorden may be cited : " An anæmic individual requires and consumes at least the same quantity of oxygen, and consequently produces the same number of calories as a healthy person. Extreme conditions that directly threaten life are, possibly, subject to other laws."

If the reasons for this phenomenon be investigated, then it is to be noted that Kraus (9, 10) had already directed attention to the greatness of the volume of air respired, and the tendency to forced respiration manifested by his patients, and, further, had laid emphasis on the fact that muscular work implies a greater respiratory stimulus and leads to an increased rate of blood-flow in the case of anæmic individuals. In agreement with these statements, von Noorden (16) therefore looks for the cause of the increased respiratory interchange, which is occasionally observed, in an augmentation of cardiac activity

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and an increase in the respiratory rhythm. Jaquet (17) lays stress on this additional fact—that anæmic persons are frequently restless during the course of the experiments in consequence of their irritability. Magnus-Levy (7) suggests that the changes which take place in the gaseous exchange during respiration possibly correspond to different phases of the disease. Although, in view of positive results, it must be admitted that an increase of the respiratory interchange does occur in cases of severe anæmia, yet a long-continued increase probably need not overstep certain definite limits, since a good or, at least, passable, panniculus adiposus is observable not only in chlorosis, but also in severe types of anæmia, notwithstanding extreme deficiency of hæmoglobin. Further, experience gained from the results of overfeeding animals has taught us that repeated blood-letting facilitates the deposition of fat.

All foundation for the view that the O_2 consumption and CO_2 output are dependent upon the number and functional capability of the erythrocytes, or upon the quantity and functional utility of the hæmoglobin, has been entirely removed by the investigations just described, and the theory of Pflüger and Voit (17), according to which the cells of the organism are the chief determining factors in the processes of combustion within the organism, has been confirmed. Further, the foregoing results, obtained by the investigation of the respiratory metabolism, render necessary a revision of the view supported at one time by Bauer (1) and A. Fraenkel (18), but recently modified by the latter (19). According to this theory, the deposition of fat in the parenchyma of different organs, which has been observed in cases of acute and chronic anæmia, is to be referred to a diminution in the processes of oxidation. For even in this field the more recent investigations [Lebedeff (20), G. Rosenfeld (21) have given occasion for alterations in former theories, so that at most an indirect connection between the diminution in the quantity of oxygen present in the blood and the occurrence of fatty degeneration may be assumed. Von Noorden (16) has given expression to this view in the conjecture that the cells as a whole or individually are injuriously affected for this reason: that, when the quantity of hæmoglobin in the blood is diminished, they are forced to perform a larger amount of work in order to supply their oxygen requirements. For Lubarsch (22), Leick, and Winckler (23) are not the only authors who look upon commencing cellular disintegration or protoplasmic degeneration as conditions which favour fatty infiltration. A whole series of investigators, including Kraus (24), Ribbert (25), and others, hold that a pathological deposition of fat only occurs in cells which have undergone a primary alteration. For this reason it may be now assumed that it is not the scarcity of oxygen, but rather the excessive effort required for procuring oxygen from blood but meagrely supplied with that gas, which produces such an alteration in the cells as predisposes them to a fatty infiltration. Further, since the fat, which is derived from the blood, is to be regarded as especially responsible for such a fatty infiltration, especial attention should now be directed to a specific relation existing between the decrease in the quantity of hæmoglobin in the blood and the metabolism of fat. Cohnstein and Michaelis (26) have shown that when air is passed through defibrinated

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dog's blood, the latter under certain conditions can transform three-fourths of the fat present in the chyle into a form which is soluble in water. On repeating this experiment with human blood and chyle, I have observed that 51 per cent. of the substances soluble in ether disappear from the blood and chyle. Since, however, according to Cohnstein and H. Michaelis, the lipolytic action of the blood is due to the presence of hæmoglobin—this lipolytic power is found in laked blood, but not in the serum—the view is consequently not excluded that, when the quantity of hæmoglobin is diminished, obstacles to the decomposition of the fat contained in the chyle may occur as a result. These obstacles may on their side facilitate fatty infiltration when an occasion for the latter is present. For this reason it appears to be a justifiable question whether the fat found in cases of fatty infiltration occurring in severe anæmia is not derived from the fat of the chyle or nutriment rather than from the fat of the tissues.

In the last fifteen years the investigation of the respiratory gaseous interchange has undergone so great a development, and our views, with regard to the importance of other indicators of the consumption of oxygen within the organism, have suffered such a transformation, that other methods of investigation employed at an earlier date in the study of the expenditure of oxygen within the organism must now be relegated to a secondary place as compared with the investigation of the gaseous interchange. Thus the quantity of uric acid present in the urine can no longer be regarded as a criterion of the extent of protein decomposition, since uric acid only indicates the metabolism of the nucleins. Further, the utilization of benzene as an indicator, with regard to which Nencki and E. Sieber (29) have noted that it is less completely oxidized to phenol in cases of leuchæmia than in healthy individuals, has yielded very variable results in the hands of Kraus and Chvostek (9). The examination of the blood [Irisawa (30)] or of the urine [von Noorden (16)] for the presence of lactic acid has yielded but little information. The like may be said with regard to the examination of the urine for sugar. Even after administering 150 grammes of glucose to a fasting individual von Noorden (16) failed to find sugar in the urine. R. Schmidt (31) obtained the same result after numerous experiments on a case of pernicious anæmia, and I can report confirmatory investigations in six cases of pernicious anæmia (as well as of ten cases of anæmia due to carcinoma) after the administration of 100 grammes glucose to the fasting patients. Paul Mayer (33) originally stated that the presence of glycuronic acid in the urine is a sign of a decrease in the power possessed by the organism of oxidizing glucose. At the present time he assumes that it can give such an indication. In my opinion, however, the appearance of glycuronic acid in the urine is not sufficiently unequivocal to serve as a basis for the consideration of the oxidation processes in the organism. I have noted (thirteen times in 350 observations) that, after the administration of 100 grammes glucose, the sugar was not excreted as such, but in the form of a lævorotatory, nonfermentable substance, and that simultaneously such large amounts of indican were frequently excreted, that I regarded the presence of abnormal quantities of paired compounds

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of glycuronic acid, especially with indoxyl and scatoxyl, as the source of the lævorotation in a large proportion of the cases examined. For this reason I should not like to draw any conclusion with regard to a diminution of the power possessed by the organism of oxidizing glucose from the fact that I obtained the foregoing results in some cases of severe anæmia.

The utilization of the quantity of neutral sulphur present in the urine does not afford us a much better criterion of the processes of oxidation. As is well known, E. Salkowski (36) and Rudenko (37) have drawn attention to the fact that an increase in the quantity of neutral sulphur at the expense of the acid sulphur may be taken as an indicator of a diminution in the oxidizing power of the tissues. Schmidt (31) found an increase in the quantity of neutral sulphur in two cases of pernicious anæmia. Schupfer and de Rossi (41) found an average of 40 per cent. of neutral sulphur in five experiments on two cases of anæmia due to anchylostomiasis. On the other hand, the values for the neutral sulphur obtained by von Moraczewski (40) in cases of pernicious anæmia lay within the normal limits, or only slightly exceeded the normal value of 20 per cent. Taylor (39) also found the low value of 6·82 per cent. in pernicious anæmia, while he recorded values varying from 12·8 to 21·5 per cent. in leuchæmia. Stadthagen (38) has likewise not succeeded in finding an increase of the quantity of neutral sulphur in cases of leuchæmia. R. Schmidt (31) found 13 to 14 per cent. in one case of chlorosis, 23 per cent. of neutral sulphur in another case. The values obtained by Vannini (75) in five cases of chlorosis varied from 13·59 to 26·80 per cent. The results of the investigations hitherto carried out are therefore but little fitted for enabling us to form definite conclusions on this subject.

II.—THE INFLUENCE OF DISEASES OF THE BLOOD ON PROTEIN DECOMPOSITION, AND ON THE METABOLISM OF PURIN BODIES AND INORGANIC SALTS.

PROTEIN DECOMPOSITION IN DISEASES OF THE BLOOD.

1. Acute Losses of Blood.

The statements with regard to protein decomposition in cases of acute losses of blood are not in agreement with one another. Bauer (1) and Jürgensen (42) have observed an increase in the quantity of nitrogen excreted by the dog after an acute loss of blood. Fraenkel (43) has also interpreted as a sign of increased tissue waste the high excretion of urea (42·17 grammes) which he found after hæmorrhage from the stomach occurring in a case of jaundice. On the other hand, von Noorden has thrown doubt on the occurrence of increased protein decomposition following severe hæmorrhages, since he did not find, either on the day of the hæmorrhage or on the days immediately succeeding it, a distinctly greater excretion of nitrogen in two cases of dangerous hæmorrhage than that originally determined for the fasting condition. Since that time several investigators have expressed their views on the question of "posthæmorrhagic azoturia." Kolisch (44) and Magnus-Levy (14) favour its existence.

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On investigating the quantity of nitrogen excreted by a man sixty-nine years old after an abundant gastric hæmorrhage, Kolisch found that on two days the nitrogen excretion amounted to 19·15 and 20·16 grammes in 1,140 and 1,600 c.c. of urine respectively, notwithstanding the fact that the patient took absolutely no nutriment during this period. He also drew attention to an observation made by E. Neusser on a patient with gastric ulcer, who excreted nearly 40 grammes of urea in the urine passed during the twenty-four hours following the hæmorrhage. Magnus-Levy found a very considerable loss of nitrogen (on one occasion 24 grammes) occurring after a copious hæmorrhage in a case of purpura hæmorrhagica. The large amount of nitrogen excreted could not be explained by any absorption of blood from the alimentary canal. It must be noted, however, that a febrile condition of several days' duration had preceded the hæmorrhage (*cf.* 45, 46, 47). Sticker and others found marked losses of nitrogen as a consequence of copious hæmorrhage from the nose occurring in a case of leuchæmia.

Ascoli and Draghi (48) have also found no "recognisable influence of the loss of blood upon protein decomposition" in the case of five persons from whom they had withdrawn 200 to 475 c.c. of blood. Yet a certain irregularity in the excretion of nitrogen becomes manifest on considering the tables given by Ascoli and Draghi. Accurate statements with regard to the supply of food are also wanting. Notwithstanding these facts, a review of their experiments appears to justify their inference. They also failed to find an increase in the quantity of nitrogen excreted by a dog on constant diet after a loss of blood amounting to 475 c.c.

For a considerable period I have myself prosecuted investigations on the metabolic changes following artificial losses of blood as well as gastric hæmorrhages, with a view to solving the problem of "posthæmorrhagic azoturia." I have at my disposal four experiments dealing with the influence of blood-letting (150 to 200 c.c.) upon metabolism, and seven experiments concerning the influence of abundant gastric hæmorrhages on the excretion of nitrogen. In the former experiments a complete balance was established; in the latter this was not carried out. Since the space at my disposal does not permit me to communicate the full details of my observations on the alterations in metabolism produced by the withdrawal of blood, I shall here limit myself to the statement that my experiments dealing with the influence of blood-letting upon the excretion of nitrogen have proved incontestably that an increase in the nitrogenous excretion does not occur as a consequence of the withdrawal of blood from the organism. On the other hand, I found very high values for the nitrogenous excretion in four out of seven cases of gastric hæmorrhage in which I estimated the quantity of nitrogen excreted in the urine, so that I also am compelled to regard a posthæmorrhagic azoturia as a possible condition. As regards the latter observations, I shall here limit myself to a recapitulation of those experiments which yielded high values for the nitrogenous excretion. I should like, however, to state that the three cases of gastric hæmorrhage in which the quantity of nitrogen excreted was not increased were no less severe than those in which there was a marked rise in the quantity of nitrogen present in the urine. The following statement gives details with regard to the latter cases.

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(*a*) Patient K., abundant gastric hæmorrhage. Recurrence of the hæmorrhage six days prior to the metabolic investigation of the case ; extreme anæmia present two days prior to the experimental investigation.

Date.	*Quantity of Urine.*	*Specific Gravity.*	*Total Nitrogen.*	*Food-supply.*
	C.c.		Gm.	
October 11, 1899	925	1024	15·54	650 c.c. of milk, 50 c.c. gelatine.[1]
,, 12 ,,	1350	1023	26·54	Ditto.
,, 13 ,,	1010	1023	16·94	One nutrient enema (200 c.c. milk, two eggs, 40 grammes glucose, 50 c.c. mixed alcoholica).
,, 14 ,,	1120	1019	14·18	—
,, 15 ,,	925	1020	9·96	650 c.c. of milk.
,, 16 ,,	*Death.*		—	—

Post-mortem examination revealed the scar of a previous ulcer, and an erosion from which the fatal hæmorrhage had originated. No blood was found in the stomach or small intestine. Solid, hard fæcal masses having the characteristic appearance due to admixture with partially decomposed blood were found in the lower part of the large intestine.

(*b*) H., forty-five years old, gastric ulcer. During his stay in the ward a fainting attack occurred, and about 1 litre of blood was vomited. The fæces were pitch-black in colour.

Date.	*Quantity of Urine.*	*Specific Gravity.*	*Total Nitrogen.*	*Food-supply.*	*Fæces.*
	C.c.		Gm.		
February 12, 1898	710	1026	15·91	Nutrient enema of bouillon plus wine.	—
,, 13 ,,	740	1027	16·57	Ditto and one nutrient enema (200 c.c. milk, two eggs, 40 grammes glucose, 50 c.c. mixed alcoholica).	Two black stools.
,, 14 ,,	700	1023	13·80	Ditto.	Three stools tinged with blood.
,, 15 ,,	630	1013	4·19	Ditto, and one cup of milk.	Fæces no longer tinged with blood.
,, 16 ,,	540	1022	9·54	One cup of milk, three nutrient enemata.	—
,, 17 ,,	940	1016	9·21	Ditto.	—
,, 18 ,,	740	1018	9·84	Ditto.	Fæces again tinged with blood.
					Fæces no longer tinged with blood.

After the quantity of nitrogen excreted in the urine had remained at this level for some days, it sank gradually until it amounted to only 2 to 3 grammes in the period extending from February 28 to death, on March 8, 1898. Post-mortem, a gastric ulcer was found.

[1] The quantity of nitrogen present in the milk at the Charité Hospital varied according to my numerous analyses from 0·36 to 0·5 per cent. The gelatin mixture which was administered contained on an average 1 per cent. of nitrogen. Over an extensive series of estimations of the quantity of nitrogen present in the urine of patients nourished solely by nutrient enemata, I have very rarely found more than 4 grammes of nitrogen in the urine passed during the twenty-four hours. As a rule, the quantity excreted was smaller

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(*c*) K., gastric ulcer. Severe gastric hæmorrhage occurred on two occasions. No symptoms of distinctive nature had been noted prior to the hæmorrhage. On admission the patient was very anæmic.

Date.	*Quantity of Urine.*	*Specific Gravity.*	*Total Nitrogen.*	*Food-supply.*	*Fæces.*
	C.c.		Gm.		
May 29, 1900	960	1023	17·8	Two nutrient enemata (200 c.c. milk, two eggs, 40 c.c. of glucose, 50 c.c. mixed alcoholics).	Black in appearance, 1125 grammes fluid.
„ 30 „	1050	1026	16·8	Two nutrient enemata, 30 c.c. gelatin (10 : 150).	Brown in appearance, 313 grammes fluid.
„ 31 „	975	1025	17·7	Ditto.	—
June 1 „	1170	1025	22·3	Two nutrient enemata, 75 c.c. gelatin.	947 grammes fluid
„ 2 „	1010	1025	20·6	Two nutrient enemata, 75 c.c. gelatin.	40 grammes fluid.
„ 3 „	1125	1022	18·4	Two nutrient enemata 75 c.c. gelatin.	570 grammes semifluid.
„ 4 „	1150	1022	18·4	Two nutrient enemata and ½ litre milk.	—
„ 5 „	1075	1021	19·2	Two nutrient enemata and ½ litre milk.	—
„ 6 „	1125	1024	21·3	Two nutrient enemata, and 75 c.c. gelatin and 1 litre milk.	270 grammes fluid.
„ 7 „	825	1025	15·8	Two nutrient enemata, and 75 c.c. gelatin and 1 litre milk.	—
„ 8 „	810	1027	16·4	Two nutrient enemata, and 75 c.c. gelatin and 1 litre milk.	580 grammes fluid.
„ 9 „	775	1025	15·0	Two nutrient enemata, and 75 c.c. gelatin and 2 litres milk.	—
„ 10 „	955	1022	13·7	Two nutrient enemata, and 75 c.c. gelatin and 2 litres milk.	—
„ 11 „	640	1018	15·6	Two nutrient enemata, and 75 c.c. gelatin and 2 litres milk.	820 grammes fluid.
„ 12 „	1270	1012	10·7	One nutrient enema, and 75 c.c. gelatin and 2 litres milk.	320 grammes fluid.
„ 13 „	810	1024	9·9	One nutrient enema, and 75 c.c. gelatin and 2 litres milk.	340 grammes fluid.
„ 14 „	850	1021	8·7	One nutrient enema, and 75 c.c. gelatin and 2 litres milk.	—
„ 15 „	1050	1025	12·4	One nutrient enema, and 75 c.c. gelatin and 2 litres milk.	425 grammes fluid.
„ 16 „	1150	1018	10·1	One nutrient enema, and 75 c.c. gelatin and 2 litres milk.	232 grammes fluid.
„ 17 „	1875	1018	15·1	½ litre coffee, ½ litre beef-tea, 2 litres milk, two eggs, ⅜ litre soup, 50 grammes gelatin.	—

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(*d*) B., fifty-one years of age, gastric ulcer. Hæmatemesis.

Date.	*Quantity of Urine.*	*Specific Gravity.*	*Total Nitrogen.*	*Food-supply.*
	C.c.		Gm.	
January, 29, 1898	350	1031	5·15	Three nutrient enemata of 150 c.c. milk, 150 c.c. beef-tea, one egg, and 50 c.c. mixture alcoholica.
,, 30 ,,	660	1027	14·44	Ditto.
,, 31 ,,	575	1026	13·8	Ditto.

On January 31 death took place. Post-mortem examination revealed the presence of a gastric ulcer.

The first of these series of investigations is of special interest, because the quantity of nitrogen excreted in one day amounted in this case to 26·54 grammes, notwithstanding the fact that the food supplied contained little more than 4 grammes of nitrogen. The other numerical values are strikingly high considering the small amount of food taken. It must be admitted, however, that one must take into account, as Kolisch has already done, the possibility that the high numerical values for the nitrogenous excretion found in cases of gastric hæmorrhage may sometimes be due to the absorption of the large quantities of blood which have passed into the intestines.

Notwithstanding this fact, the material at present available seems at least to indicate the possibility of a "posthæmorrhagic azoturia," which, however, only appears to occur after excessive hæmorrhage, and even then not invariably. Its appearance or absence is probably dependent on the varying power of resistance exhibited by the organs of different individuals to the injurious influence exerted by severe losses of blood. The fact that it is absent as a rule after the withdrawal of quantities of blood, which do not exceed a certain limit, is not without importance in the therapeutical applications of blood-letting, since an increase of protein decomposition is not desirable in many cases in which the withdrawal of blood is indicated (*e.g.*, acute infectious diseases and inflammatory renal conditions).

2. Chronic Forms of Anæmia.

A description of protein decomposition in chronic types of anæmia necessitates the separate consideration of the conditions found in anæmia gravis, in chlorosis, and in the various forms of leuchæmia.

In the case of anæmia gravis the types of anæmia produced by helminthes must be distinguished from the so-called cryptogenetic forms, since in the case of the former—at least, in anæmia due to bothriocephalus, and certainly, also, in that due to anchylostoma—toxic influences have to be considered. The presence of such toxic influences increases the difficulty of finding a reply to the question as to what, in concrete instances, is the consequence of the anæmia *per se*, and what the result

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of the actively toxic factor generated in the intestine. For this reason, those observations which have been made in the case of the cryptogenetic forms of anæmia gravis will be here described prior to those which have been established in the case of the forms of anæmia due to helminthes.

Amongst the earlier investigators, Eichhorst and Quincke (50) stated that an increased protein decomposition occurs. On the other hand, H. Müller (51), Ferrand (52), Scheperlen (53), and Hansen (54), maintain that the quantity of urea excreted was diminished in the cases examined by them. Laache (55) also believed that an increased breaking down of protein did not take place in the cases investigated by him. In the case of a patient suffering from pernicious anæmia, who was so poorly nourished that he might be regarded as being practically in a fasting condition, Kraus (10) found values for the excretion of nitrogen to vary from 5·37 to 7·46 grammes. These values do not appear to indicate an increased decomposition of protein. The foregoing investigations, as well as a series of similar nitrogen estimations carried out by G. Honigmann (56), suffer from the absence of corresponding estimations of the nitrogen in the fæces. Further, albuminuria was also present as a complication in one of the patients examined by Laache.

Von Noorden (57) was the first to carry out accurate metabolic investigations upon patients suffering from pernicious anæmia. From these experiments, in which all the factors necessary for an accurate balance-sheet were included, he was unable to convince himself that protein decomposition was increased as a consequence of anæmia. For this reason von Noorden definitely opposed the theory that severe forms of anæmia lead, as a rule, to an increase in the quantity of protein broken down. Von Noorden's view has since received support from different authors.

Neusser (58) first reported a case of pernicious anæmia in which the quantity of nitrogen excreted was approximately proportional to that taken in as food. His experiments extended over a period of three days. Unfortunately the estimation of the nitrogen in the fæces was omitted in this research. On the other hand, Moraczewski (40) determined the fæcal nitrogen, and although the significance of many points in his results is not quite clear, yet, on considering his results as a whole, the tendency to the retention of nitrogen was greater in his cases than that to an increase in the quantity of nitrogen excreted. It must be noted, however, that albuminuria was present in one of the cases examined by him. Since von Moraczewski observed that nitrogenous equilibrium was established in his cases on a nitrogen excretion amounting only to 6 to 7 grammes, he therefore interpreted this phenomenon as an "apathetic condition" of the organism in relation to the decomposition of protein. Stejskal and Erben have shown that this explanation is unnecessary, since the patients examined by Moraczewski were partially undernourished. Von Stejskal and Erben (59) have also found a retention of nitrogen as the result of an investigation carried out in a case of pernicious anæmia over a period of four days. I myself (60) have been able to demonstrate the same point in two cases of pernicious anæmia. I extended the period of investigation over ten days in the first case, and

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over four days in the second. Further, I found in a third case, in which I did not find it possible to estimate the nitrogen in the fæces, such low results for the total nitrogen on two days that these cases at least do not appear *a priori* to favour the view of an increased decomposition of protein. Bloch (61) has recently come to the like conclusion as the result of similar investigations. In an experiment extending over six days, he found in one case of pernicious anæmia a retention of nitrogen amounting to 3·08 grammes per day. It is to be noted that the nitrogen intake (17·8 grammes) was high in this case. In a second case of pernicious anæmia with severe atrophy of the intestinal glands, he found, as the result of experiments extending over ten days, a daily retention of nitrogen amounting to 1·8 grammes on an intake of nitrogen of 17·23 grammes.

It must be admitted that the results of an investigation carried out by Rosenqvist (62) are to some extent in opposition to the foregoing observations, although the differences between the two series of results are not insurmountable. In an exceedingly careful piece of work this author estimated the nitrogen balance in three cases of the cryptogenetic type of pernicious anæmia, and found, as a result, that periods during which the excretion of nitrogen was increased alternated with those in which a retention of nitrogen occurred. Rosenqvist's results, however, are not directly comparable with those obtained by the authors just mentioned. For Rosenqvist founded his views on a so-called daily balance, while the authors just named laid special stress on carefully scrutinizing as a whole the results of a prolonged series of experiments. Rosenqvist obtained his daily balance-sheet by an accurate comparison of the daily food-supply with the quantity of nitrogen excreted in the urine. The quantity of nitrogen excreted per day in the fæces was calculated, not directly estimated. As a result of this method of procedure, he found very considerable variations in the excretion of nitrogen on examining eighteen cases of anæmia due to bothriocephalus. In some cases he was able to determine a well-marked loss of nitrogen during the period in which the worm was present in the body, while, after its extrusion, a retention of nitrogen was usually demonstrable. Rosenqvist came to the conclusion that a pathological decomposition of protein was also present in the cases of the cryptogenetic form of pernicious anæmia examined by him. In forming this opinion he appears to have been influenced to some extent by the observations which he had previously made in the case of anæmia due to bothriocephalus. The justification for such a theory, however, is disputable, for the variations in the excretion of nitrogen occurring in cases of the cryptogenetic form of anæmia, which have been observed in one instance by Strümpell, in others by von Moraczewski, von Stejskal, Erben, and myself, are also explicable in another way. I have elsewhere called special attention to the fact (28), upon which F. Umber (62A) since then has also laid stress, that there is a liability to error involved in the method adopted by Rosenqvist of calculating the daily excretion of nitrogen in the fæces as the mean of the total quantity of nitrogen present in fæces collected for a series of days—in some instances for more than a week. For it is

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obvious that such temporary functional disturbances might occur in the alimentary canal in consequence of severe anæmia as would lead to variations in the amount of material absorbed per diem, and it is also quite possible that in a larger or smaller proportion of cases more or less protracted disturbances of the renal functions might be produced by the anæmia, which would lead to such irregularities in the excretion of nitrogen as are found in patients suffering from renal disease. At any rate, von Koranyi (63) and Kovacs (63A) have already found such conditions in cases of severe anæmia, and I myself have repeatedly observed disturbances of the renal functions, which showed a more or less marked similarity to those occurring in chronic forms of nephritis. Disturbances of the nature described serve not only to explain any temporary increase in the excretion of nitrogen, but also any temporary retention of nitrogen, if the pathological deviations referred to do not reach too high a degree. As regards the retention of nitrogen, there must also be considered, in this connection, a possibility, suggested by Bernert and von Stejskal (64), that a retention of nitrogen may frequently be merely a consequence of previous underfeeding.

The foregoing opinions, which have been expressed on the question of the pathological decomposition of protein, are not intended to throw doubt on the occurrence of a pathological breaking down of protein in the forms of anæmia due to helminthes. Such an intention would be doomed to failure at the outset, since Bohland (65) and Vannini (65A) have definitely established a pathological loss of nitrogen in cases of anæmia due to anchylostoma. Schupfer and de Rossi (41), as well as von Jaksch (66) (examination of the fæces is absent from the investigations of the latter), have, however, supposed that they could exclude such a decomposition of protein. An account has already been given of the results obtained by Rosenqvist in anæmia due to bothriocephalus. The following conclusions of Rosenqvist, however, deserve special attention. He regards the breaking down of protein which occurs in anæmia due to bothriocephalus as a consequence of the toxic action of the worm rather than a result of the anæmia *per se*. In fact, he definitely states that the poison formed by *Bothriocephalus latus* injures not only the red blood-corpuscles, but also the protoplasm of other tissues. In another place Rosenqvist states: "Anæmia as such does not give rise to increased protein decomposition. Anæmia *per se* exerts no directing influence upon protein metabolism." These remarks of Rosenqvist deserve special attention, since they have not received sufficient consideration in the literature of the subject.

The fact that even the most severe types of chronic anæmia may often run their course for a considerable period without injury to the protein constituents of the organism should not excite surprise, if it is remembered that the organism readily adapts itself to the action of injurious influences, if these make themselves only slowly felt with gradually increasing intensity. Yet the possibility should not be denied that a pathological increase in the excretion of nitrogen may at times occur in the course of diseases of the blood in consequence of the sudden destruction of large masses of blood-corpuscles. An occurrence of this

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nature is exemplified by a case of anæmia observed by Kolisch and von Stejskal (67), which had commenced as a pseudo-leuchæmia, and in which they were able to determine a nitrogen excretion of 18·63 to 24·29 grammes on a nitrogen intake of 1·6 to 7·7 grammes. The increase of protein decomposition indicated by the marked rise in the nitrogen excretion was found to run parallel with a rapid destruction of red blood-corpuscles (their number sank within four days from 2,200,000 to 800,000). Kolisch and von Stejskal interpreted this exceptionally large excretion of nitrogen as a "phthisis of the blood." Such a theory appears very plausible. At the same time it seems justifiable to consider the question as to whether a destruction of other cell substances induced by the same toxic agent did not also occur along with that of the red blood-corpuscles.

Umber (62A) has also demonstrated a pathological decomposition of protein in a case of anæmia occurring in Banti's disease; he refers this not to the anæmia *per se*, but—since the pathological decomposition of protein disappeared after removal of the spleen—to a toxic agent produced in the diseased spleen, which not only caused the anæmia, but also affected the general metabolism of the organism. Since Umber found a retention of nitrogen in another case with similar clinical symptoms, he therefore defined the former case as a "toxic anæmia of splenic origin." Bernert and von Stejskal (64) have made special investigations with regard to the quantity of nitrogen required for the attainment of nitrogenous equilibrium. They were able to attain nitrogenous equilibrium on 4·04 grammes of absorbed nitrogen contained in a dietary which yielded 34 calories per kilogramme. They conclude from this fact that cases of pernicious anæmia can be maintained in nitrogenous equilibrium on approximately the same small quantity of protein as normal individuals.

Investigations by F. Müller and others (68 to 75) are available for a critical consideration of the protein decomposition in *chlorosis*. The quantities of nitrogen present in the urine and the fæces were not estimated in the investigations carried out by Schücking and Setti. Monari calculated the nitrogen from von Noorden's tables (!) and von Moraczewski also does not appear to have calculated *ad hoc* the amount of nitrogen contained in the food taken in each one of his cases. For this reason the works of Müller, Lipman-Wulff, Henius and Vannini are alone available for the present purpose. In Müller's investigation a slight loss of protein (of 1·2 grammes per day) occurred at the close of a period of six days on a daily average protein intake of 16·5 grammes. Such a loss of protein, however, did not occur in the three cases examined by L. Lipman-Wulff, as well as in the case examined by Henius. On the contrary, nitrogenous equilibrium was found to be maintained throughout the experiments of these authors. Vannini found a slight nitrogen retention in three instances, approximate nitrogenous equilibrium in one instance, and a slight nitrogen loss in another case. The view held by von Noorden (76), that protein metabolism is absolutely normal in ordinary cases of chlorosis, may therefore be supported. This fact is not without theoretical importance, since an attempt has been made by different authors to regard toxic factors as responsible for the development of chlorosis.

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Numerous investigations have been made upon protein decomposition in leuchæmia. An accurate estimation of the results of many of the researches is rendered difficult by the shortness of the periods, the lack of accurate determinations of the food intake, and complications, such as fever, hemorrhage, etc. Thus, for example, the investigation of Pettenkofer and Voit (6), in which nitrogenous metabolism was fairly normal, extended over a period of only one day. The same objection is valid for Ebstein's case (77), the patient excreting 62·75 grammes of urea on the day immediately preceding death, notwithstanding his condition of extreme inanition. Estimations of the amount of nitrogen present in the fæces were omitted in the investigations carried out by Sticker (45), Bohland and H. Schurz (78), Munzer (79), R. Stüve (80), and partially also in those of Magnus-Levy (14). As regards Sticker's observations, it must, however, be admitted that their long duration (eight months) makes amends for many defects due to the omission of the examination of the fæces. The conditions in Magnus-Levy's cases were also so clear that no objections can be raised to the conclusions of this author. The same statement may likewise be made with regard to Stüve's investigation. Bearing these points in mind, it is possible to broadly distinguish the cases of acute from those of chronic leuchæmia.

On considering three cases of acute leuchæmia, in which Magnus-Levy (14) has examined the excreta, it becomes manifest that the disease is characterized by a great tendency to a diminution of the protein contained in the organism.

Magnus-Levy repeatedly noticed a nitrogenous excretion which exceeded the intake, in some instances, by as much as 40 grammes per day. May (46), v.d., Wey (47) (Case I.), and others, including Ebstein, made similar observations on patients at a period immediately prior to their death.

In chronic leuchæmia the tendency to increased decomposition of protein is not such a marked feature. Although extensive protein decomposition was demonstrable in a case investigated by Fleischer and Penzoldt (81), and although a considerable loss of protein was also apparent in the case of Sticker's patient, yet Bauer and Reihlen (82), and others (14, 16, 38, 47, 83, 84, 85) did not observe any nitrogen loss in cases of chronic leuchæmia. Matthes (86) even found a slight retention of nitrogen in a case which was doubtless to be regarded as chronic leuchæmia.

Von Stejskal and Erben also observed such a retention in a case of chronic leuchæmia, while in their case of myelogenous leuchæmia nitrogenous equilibrium was not attainable notwithstanding an abundant protein intake. The latter statement is corroborated by Stuves's (80) observations on a case of chronic lymphatic leuchæmia, yet the presence of œdema has to be borne in mind in the consideration of this case of lymphatic leuchæmia as well as of a similar case observed by von Stejskal and Erben. On the whole, a critical examination of all the conditions involved in this question yields the impression that the excretion of nitrogen approximately corresponds to the intake as food in the case of the torpid forms of chronic leuchæmia, unless complications such as

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extensive hæmorrhages, febrile conditions, etc., are present as marked features of the disease. It seems justifiable, however, to inquire whether an increase in the nitrogenous excretion directly connected with the disease itself may not occur in certain phases of the illness. One is led to consider such a possibility for this reason amongst others that, even in the case of chronic forms of leuchæmia, variations in the intensity of the pathological process lead to periods which show a greater or less similarity to the clinical picture of acute leuchæmia. A definite decision on this question can admittedly only be possible in the light of a fuller knowledge of the causes of leuchæmia than is yet available. Variations in the nitrogenous excretion may, however—in a similar fashion to that already described in connection with pernicious anæmia—also be due to functional disturbances affecting the alimentary canal or kidneys, because it is definitely known that these organs sometimes show anatomical alterations in cases of leuchæmia. In many cases an increase in the excretion may also occur as a consequence of an abnormal destruction of leucocytes, since quantities of uric acid exceeding 6 to 8 grammes per day have been repeatedly observed in these cases. Sticker has directed attention to a certain parallelism existing between the amount of nitrogen excreted and the number of leucocytes formed, and it will be evident from the following chapter to what an extent the destruction of leucocytes is to be regarded as responsible for an increase in the excretion of nitrogen in the urine.

METABOLISM OF THE PURIN BODIES.

The knowledge gained in the last ten years of the close connection between the breaking down of cell nuclei and the excretion of purin bodies—especially of uric acid—in the urine lends a greater interest than formerly to estimations of the quantity of the purin bodies and of uric acid present in the urine of cases of anæmia and of leuchæmia. The reliability of the methods employed and the nature of the diet given must both be carefully borne in mind. As regards the first point, the results obtained with the aid of the Krüger-Wulff process cannot be included, since many sources of error have been demonstrated in this method. Amongst these sources of error, the influence of albumoses in the urine upon the experimental results of this method, which has been demonstrated first by myself (88), then by Salkowski (125), and by Flatow and Reitzenstein (89), here deserves attention. Further, at the present time we can only regard the method of Ludwig-Salkowski, or such methods as are founded on the same, or, at least, on a similar principle, as reliable for the estimation of uric acid. When possible, the diet should be purin-free. Although the latter condition must be regarded as essential, in the present connection there are some investigations in which the peculiar character of the experimental conditions, and the knowledge of the composition of the diet, permit certain conclusions to be drawn. We shall now describe the anæmic and leuchæmic conditions separately, and consider the estimations of uric acid prior to those of the purin bodies, since the available number of reliable estimations of the former is much greater than those of the latter.

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1. Forms of Anæmia.

My own investigations dealing with the action of repeated blood-letting have yielded the following figures as regards the consequences of acute losses of blood upon the excretion of uric acid :

Name.	*Diagnosis.*	*Day of the Withdrawal of Blood—*		*Average Numerical Result of the Withdrawal of Blood—*	
		Before.	After.	Before.	After.
		Uric Acid Nitrogen.	Uric Acid Nitrogen.	Uric Acid Nitrogen.	Uric Acid Nitrogen.
		Gm.	Gm.	Gm.	Gm.
S.	Amyotrophic lateral sclerosis	0·410	0·367	0·425 (4 days)	0·365 (2 days).
K.	Traumatic neurosis	0·231	0·258	0·259 (3 days)	0·272 (3 days).
M.	,, ,,	0·246	0·281	0·278 (3 days)	0·280 (5 days).
K.	Diabetes levis	0·588	0·323	0·425 (4 days)	0·365 (2 days).

Neither on the day on which the blood was withdrawn nor on the succeeding days can any distinct effect on the excretion of uric acid be deduced from the foregoing figures, which are directly comparable with one another, since the diet given to the patients was invariably the same. Amongst the cases of posthæmorrhagic anæmia I have traced for a period of sixteen days the excretion of uric acid in the case of the patient K., concerning whom details are given on p. 358. I found on the second day an excretion of nitrogen in the form of uric acid amounting to 0·136 gramme. The corresponding quantity excreted on the third day was 0·418 gramme, and on the fourteen succeeding days the average excretion amounted to 0·219 gramme, the minimal being 0·136 gramme and the maximal 0·358 gramme. Throughout the foregoing period the diet was purin-free, consisting of nutrient enemata as well as of milk and gelatin administered by the mouth. The quantity of uric acid nitrogen was 0·182 gramme on the last day of the investigation in the case of B., to whom nutriment was given per rectum.

I have examined two cases of severe chronic anæmia due to repeated small hæmorrhages. On a purin-free diet the average of a three-days experiment was 0·212 gramme in the one case (gastric ulcer) and 0·111 gramme in the second case (rectal hæmorrhage). Jacob and Bergell (90) record similar average values.

On a series of earlier estimations dealing with the secretion of uric acid in cases of anæmia gravis, *vide* Strümpell (91) (Heintz's method), H. Quincke (90), Laache (55), von Noorden (18), and others. The twenty-four hours' excretion of uric acid was within normal limits in some of these cases, in others higher than normal. The values, which von Noorden and O. Voges (92) found in cases of anæmia gravis, varied between 0·02 and 0·75 gramme uric acid nitrogen. The following observers found relatively low values for the excretion of uric acid.

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Kolisch and von Stejskal (67) found 0·089 gramme (average excretion over three days), Richter (93) 0·13 gramme (average excretion over five days) and 0·139 gramme (average excretion over six days), Brandenburg (94) 0·131 gramme (average of five days), Jacob and Bergell (90) 0·203 gramme (average of six days), and Taylor (39) 0·134 gramme. The diet of the patients examined by Kolisch and von Stejskal consisted of eggs, milk, and 200 to 400 grammes of soup. On the other hand, von Noorden and Voges, Richter, Brandenburg, Jacob and Bergell and Taylor make no definite statements with regard to the diet given. The high numerical results were found to occur, although not regularly, yet specially in the case of such patients as showed a high value for the total excretion of nitrogen. Case I. of the two patients examined by Schmidt (31) excreted an average amount of 0·293 gramme uric acid nitrogen (average of nine days), the minimal quantity excreted being 0·105 and the maximal 0·541 gramme. The average amount of uric acid nitrogen excreted by patient II. was 0·291 gramme (average of three days). The diet of both patients consisted of milk, eggs, veal, beefsteak, fowl, and cutlets. Von Stejskal and Erben (59) found in their case an average excretion of 0·195 uric acid nitrogen (average of four days) on a diet which invariably contained less than 100 grammes of meat and no soup. I myself (60) observed in one case (ten days) an average excretion of 0·351 gramme of uric acid nitrogen (minimum 0·268 gramme uric acid nitrogen, maximum 0·429 gramme uric acid nitrogen). In a second case the corresponding figures were 0·277 (average of four days), and in a third case 0·175 gramme (average of three days). One hundred grammes of minced meat and 600 c.c. of beef-tea were contained in the diet of Case I., only 60 grammes of minced meat in that of Case II. I do not possess the corresponding data concerning the diet of Case III. Bloch (61) also found the quantities of uric acid excreted "usually normal."

Rosenqvist (62) found that the average quantity of uric acid nitrogen excreted on a purin-free diet by eleven patients suffering from anæmia due to bothriocephalus varied between 0·051 and 0·281 gramme. In eight instances the average values were below 0·20 gramme. The highest value observed by Rosenqvist in his investigations was 0·291 gramme. Rosenqvist also made five series of experimental observations on three patients suffering from the cryptogenetic type of pernicious anæmia, and found 0·146 gramme as the lowest average value for the uric acid nitrogen, 0·334 gramme as the highest. The lowest value actually observed in the case of these three patients was 0·219 gramme, while the highest was 0·388 gramme. The three patients were all on a purin-free diet.

J. Loewy (95) carried out a research on a patient suffering from anæmia splenica (diet, purin-free). Diarrhœa was present during the first day of the investigation. The average amount of uric acid nitrogen was 0·109 gramme (average of three days), while, after 232 grammes of minced meat had been given, the average amount excreted was in one instance 0·180 gramme (average of three days), in the second instance 0·121 gramme.

When the foregoing results are reviewed, it is at once obvious that

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Rosenqvist's observations specially claim attention, and may be held to furnish a standard, with the aid of which the value of other investigations, carried out on a diet which was not purin-free, may be gauged. The following conclusions may be drawn from such a review. In the majority of cases the values for the excretion of endogenous uric acid are not higher than the normal [Burian and Schur (96), Sivén (97), and others]. In the other cases, the excretion is scarcely ever more than double the normal, even in those exceptional instances in which a higher excretion does occur. According to Rosenqvist, uric acid excretion in cases of pernicious anæmia shows greater variations in different individuals than occur in healthy persons maintained on a diet free from purin bodies. This fact is not surprising when it is remembered that the urinary uric acid is the product of different processes, one or the other of which may be more or less influenced by severe degrees of anæmia.

Voges (92) and F. Friedrichsen (98) found that the uric acid nitrogen excreted by chlorotic patients varied from 0·12 to 0·28 gramme. Von Noorden (76) obtained 0·22 gramme uric acid nitrogen per day in a case of severe chlorosis. Von Moraczewski (99) found in eleven cases 0·26 gramme (Haycraft's method). These results, which were obtained after administration of dietaries containing purin bodies, are so low that they prove *a fortiori* that the quantities of uric acid excreted by chlorotic patients are rarely, and even then only slightly, higher than normal. As a net result of the consideration of these investigations, it appears that the various forms of anæmia do not *per se* occasion an increased uric acid output, any increase being due rather to special factors. In cases of poliocythæmia associated with enlargement of the spleen, Weintraud found no essential increase in the urinary uric acid, 0·3 of uric acid nitrogen forming the average twenty-four hours' excretion. From the standpoint of the accuracy of the methods employed, the experiments of Schmidt (31) (Haycraft's method), Taylor (39), (Salkowski's method), Rosenqvist (62) (Arnstein and Camerer's method), and Halpern (100) (Camerer's method) need only be cited.

Schmidt found in his Case I. a daily average excretion of purin bodies calculated as hypoxanthin amounting to 1·313 grammes= 0·547 gramme nitrogen excreted in the form of purin bodies (average of eleven days), and an excretion of xanthin bases amounting to 0·260 gramme=0·11 gramme nitrogen (average of ten days). In his Case II. the corresponding figures were 1·402 grammes of purin bodies= 0·584 gramme purin nitrogen, and 0·517 gramme xanthin bodies= 0·216 gramme of basic nitrogen. Taylor found 0·021 gramme basic nitrogen, and Rosenqvist, in his case of anæmia due to bothriocephalus, found from 0·190 to 0·328 gramme nitrogen (minimal value 0·143, maximal value 0·472). All Rosenqvist's patients were on a purin-free diet. In cases of the cryptogenetic form of pernicious anæmia the purin nitrogen varied from 0·175 to 0·409 gramme nitrogen (minimal value 0·153 gramme, maximal value 0·508 gramme). Marked variations in the excretion were demonstrable in both series of observations. The average purin nitrogen excreted in a case of anæmia splenica on a purin-free diet, examined by Halpern, under my direction, was 0·253 gramme

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(average of three days), and in a case of severe secondary anæmia to 0·1988 gramme (average of three days) on an ordinary mixed diet. In a case of anæmia due to Banti's disease, Umber (62A) found a periodic variation in the excretion of urinary purin nitrogen. In this case, however, the amount excreted only slightly exceeded the upper limits for the normal excretion. The patient examined by Umber was kept on a purin-free diet (the maximal value for the excretion of purin nitrogen amounted to 0·258 gramme in the case of this patient). The values for the purin nitrogen varied from 0·126 gramme to 0·251 gramme in a case of anæmia splenica complicated with ascites (purin-free diet). According to Umber, this case was not to be regarded as belonging to the group of toxic anæmias of splenic origin. No periodicity was to be observed in the variations in the excretion of nitrogen present in this case. If 0·12 to 0·21 gramme be taken as the normal value for the endogenous alloxuric nitrogen, the excretion of purin bodies was increased in a number of cases, but by no means in all. In drawing this conclusion it must be borne in mind that, according to M. Kaufmann and L. Mohr (10), the normal value may be slightly exceeded even under normal conditions. The foregoing values for the purin nitrogen do not show any distinct parallelism with the total quantity of nitrogen excreted.

In Rosenqvist's experiments the ratio of the uric acid nitrogen to the purin nitrogen was altered on several occasions in the sense that the uric acid nitrogen formed a distinctly smaller proportion of the purin body nitrogen than under normal conditions. Schmidt found the ratio of the purin bases nitrogen to the uric acid nitrogen = 1 : 2·66 in Case I., and = 1 : 1·35 in Case II. Taylor found the ratio = 1 : 6·4 in a case of anæmia gravis, and = 1 : 11·3 and = 1 : 7·5 respectively in two cases of simple chronic anæmia. The ratio was equal to 1 : 6·5 in a case examined by Magnus-Levy (14), 1 : 2·92 in a case investigated by O. Loewi (102), and 1 : 20·5 and 1 : 9·16 in two cases examined by Galdi (103).

2. Forms of Leuchæmia.

The number of estimations of uric acid which have been carried out during a considerable period on cases of leuchæmia with the aid of Ludwig-Salkowski's method have a special interest in this connection, since, as is well known, Horbaczewski (104) and others have maintained that the decomposition of the nucleins within the body exercises a distinct influence upon the quantity of uric acid excreted in the urine. In this instance, just as in that of protein decomposition, it is important first to consider the question whether acute processes are subject to other conditions in regard to the excretion of nitrogen than those which are found to hold good for the chronic forms. It is also interesting to consider the question whether an essential difference exists between the lymphatic and myelogenic types of leuchæmia.

Ebstein (77) found a value of 0·44 gramme for the uric acid nitrogen in a case of acute leuchæmia on the day preceding death. Fraenkel (105) observed that the values for the uric acid nitrogen varied from 0·25 to

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0·51 gramme during a period of six days in which fever was absent. Magnus-Levy (14) found a value of 2·91 grammes of uric acid nitrogen in one case on the day preceding the death of the patient. This case was examined for a period of only two days. The diet consisted of milk and small quantities of soup. He found an average daily excretion of uric acid nitrogen amounting to 0·655 gramme; in another case, which was investigated during a period of sixteen days, the minimal excretion amounted to 0·41 gramme, and the maximal to 1·11 grammes. He found also an average value of 0·523 gramme of uric acid nitrogen in a third case which was investigated for a period of ten days. The minimal value in this instance amounted to 0·283 gramme, and the maximal to 0·807 gramme. At an earlier date a series of authors [Huss (106), C. Bartels (107), S. Laache (55), Ebstein, and others] found values of 3 to 5 grammes for the uric acid excretion (Heintz's method) in cases of chronic leuchæmia, yet Fleischer and Penzoldt (81), F. Mosler (108 and 109), Hoffmann (110), Schmuziger (14), G. Sticker (345), J. Bauer and Reihlen (82), Jacubasch (112), and others, have also noted low values—*i.e.*, values which only slightly exceed the normal amount. Salkowski (113) found an average value of 0·369 gramme of uric acid nitrogen in a case investigated for a period of ten days, and Stadthagen (38) 0·43 to 0·669 gramme. Bohland and Schurz (78), using Fokker's modification of Salkowski's method, found values of 0·466, 0·260, and 0·656 gramme for the uric acid nitrogen in three cases, which were investigated during periods of three, seven, and ten days respectively. Matthes (86) observed an excretion of uric acid nitrogen amounting to 0·22 gramme (average of two days) in his case, which has already been mentioned. Jacob and Krüger (114) found in a case of myelogenous leuchæmia an average value of 0·335 gramme for the uric acid nitrogen (period of eleven days). A rise in the excretion of uric acid was absent in a case examined by Weintraud (115). Richter (93) made a similar observation in a case of myelogenous leuchæmia during a period of eleven days, during which fever was absent (average daily excretion of uric acid nitrogen = 0·296 gramme). Kühnau (116) found, as the result of observations on two cases of myelogenous leuchæmia, values ranging from 0·497 gramme to 1·09 grammes for the uric acid nitrogen excreted in Case I. (fifty-nine days); while the corresponding values in Case II. (thirty-six days) varied from 0·331 to 0·737 gramme. Bondzynski and Gottlieb (117) found an average value of 0·224 gramme for the uric acid nitrogen in a mixed form of leuchæmia (minimal value 0·1650 gramme, maximal 0·3646 gramme—fifteen days' experiment). Taylor (39) found in one of his cases 0·743 gramme, and in another case a value of 0·300 gramme uric acid nitrogen. Magnus-Levy (14) records 0·227 gramme uric acid nitrogen in a case of myelogenous leuchæmia during the last twenty days of life. Wey (47) found 0·455 gramme uric acid nitrogen (average of twenty days) during a serious phase in the course of a case of myelogenous leuchæmia. The diet given was free from meat. In a second case of myelogenous leuchæmia, which was not kept on a diet free from meat, the uric acid nitrogen was 0·336 gramme. In a case of myelogenous leuchæmia von Stejskal and Erben (87) obtained 0·354 gramme uric acid nitrogen, and in a similar

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case O. Loewi observed a variation from 0·267 to 0·465 gramme of uric acid nitrogen on a fixed diet during a period of twenty-one days. Moraczewski found 0·157 gramme (average of six days), Mohr and Salomon (118) observed 0·3 gramme uric acid nitrogen in one instance and 0·4 in another. Kaufmann and Mohr found in three cases of myelogenous leuchæmia kept on a diet free from purin bodies average values of 0·3 gramme (four days), 0·328 gramme (eight days), and 0·348 gramme (two days) for the uric acid nitrogen. White and Hopkins (119) obtained an average of 0·363 gramme in a similar case. Schmid (120), in a case of mixed leuchæmia, which was not influenced by the action of drugs, found that the uric acid nitrogen varied over a series of days from 0·302 to 0·449 gramme. Galdi (103) records in a case of myelogenous leuchæmia, maintained for four days on a mixed diet, an average daily excretion of 0·483 gramme of uric acid nitrogen, and in a second similar case an average of 0·334 gramme (four days). The average amount of uric acid excreted per day in the fæces amounted to 0·0057 gramme in the first case, and to 0·011 gramme in the second case.

Gumprecht (121) noted an average value of 0·295 gramme for the uric acid nitrogen (average of seventeen days) in a case of lymphatic leuchæmia which ran a subchronic course. In the case of the chronic forms, Stüve (80) found a value of 0·216 gramme (average of twelve days), Magnus-Levy (14) one of 0·27 to 0·33 gramme (average of nineteen days) and von Stejskal and Erben (87) one of 0·232 gramme (average of five days).

Eichhorst (122) observed in the case of pseudo-leuchæmia values which varied during one period of four days from 0·01 to 0·1 gramme of uric acid nitrogen, and in another period from 0·02 to 0·46 gramme. Jolles (123) reports in one instance a value of 0·289 gramme for the uric acid nitrogen, and Kuhnau and Weiss (124) state that in one case the uric acid nitrogen varied, during a period of nineteen days, from 0·069 to 0·226 gramme, and in another case, which ultimately changed into lymphatic leuchæmia, during a period of thirty days from 0·202 to 0·429 gramme (the latter value, however, was found in the terminal stage of the disease). In a case examined by Moraczewski the excretion of uric acid nitrogen amounted to 0·177 gramme on an average taken over seven days.

On reviewing these numbers, it is evident that the figures expressing the quantity of uric acid nitrogen excreted comparatively rarely exceed the upper limit of such values as may be found under normal conditions. A marked rise appears to occur, especially in cases in which a part is played by factors associated with the moribund condition. A comparison of the number of leucocytes given in the different cases with the figures for uric acid nitrogen does not indicate any parallelism between the two, even if a keen look-out be kept for any parallelism between an increase in the uric acid and a fall in the originally high number of leucocytes. High values for the excretion of uric acid are associated not only with large numbers of leucocytes, but also with relatively small numbers (several cases of Magnus-Levy). Neither does a complete parallelism exist between the extent of the disintegration of leucocytes

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and the quantity of uric acid excreted in the urine in cases of the destruction of leucocytes produced by the Röntgen rays. (For the effect of the Röntgen rays upon the urine, consult references 124A and 124B.)

In this connection the fact is of interest that Ebstein (124C) and Weintraud (124D) met with urolithiasis in cases of myelogenous leuchæmia. I myself (124E) made a similar observation in a case of lymphatic leuchæmia in which a relative increase occurred in the number of lymphocytes without any considerable increase in the leucocytes as a whole. Urolithiasis has also been occasionally (twice in nineteen cases) observed in poliocythæmia associated with splenic enlargement, as Weintraud's summary shows. A leucocytosis existed in both Weintraud's cases (124C).

In considering the xanthin bases, Stadthagen (38) found in a case of myelogenous leuchæmia, as the result of seven estimations, an average quantity of xanthin bases precipitated as silver compounds amounting to 0·7 gramme per day. Taylor (39) found in two cases of myelogenous leuchæmia 0·066 gramme xanthin nitrogen in the first case, and 0·040 gramme in the second case (Salkowski's method). In chronic myelogenous leuchæmia Magnus-Levy estimated that 10·04 grammes xanthin bases were excreted during the last twenty days of the patient's life (Salkowski's method). Loewi (102) determined 0·102 to 0·106 gramme (period of observation three days) in one instance, and from 0·112 to 0·188 gramme during another period of three days (Camerer's method). Stejskal and Erben (87), in their case of myelogenous leuchæmia, found 0·04 gramme of xanthin (average of five days), and in their case of lymphatic leuchæmia 0·048 gramme xanthin. Kaufmann and Mohr's (101) average numbers varied from 0·043 gramme nitrogen in the form of bases to 0·076 gramme. In a case of myelogenous leuchæmia Schmidt (120) found, with the aid of a method, devised by Krüger and himself, of precipitation of the bases as copper compounds, values for nitrogen in the form of bases amounting to 0·027 and 0·028 gramme. Galdi (103) observed in one case of myelogenous leuchæmia 0·071 gramme xanthin bases (average of four days), and in another similar case an excretion amounting to 0·111 gramme [Salkowski]. Under my direction Halpern (100) found an average value of 0·297 gramme nitrogen in a case of lymphatic leuchæmia during two days in which the diet was free from meat, and on three days in which the diet contained meat an average value of 0·304 grammes nitrogen.

If these values are compared with those of healthy individuals, which amount to 25 to 32 milligrammes according to Stadthagen (38), 27·2 to 38·8 milligrammes and 51·1 to 55·1 milligrammes respectively according to Salkowski (125), 15·6 to 45·1 milligrammes according to Flatow and Reitzenstein (89), and 80·3 to 85·9 milligrammes according to Carlyle Pope (126), the values previously given may be regarded as high in the majority of cases. In this respect these figures confirm the results obtained by earlier observers, who, as a rule, found the xanthin bases greatly increased in cases of leuchæmia (127-132). Yet the results show distinctly that the organism of a patient suffering from leuchæmia has ways and means at its command for carrying the process of decomposition

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of the nuclein bodies in part beyond the stage of the purin substances. As has already been mentioned in connection with the discussion of the excretion of uric acid, a diminution in this function appears especially to occur in cases in which the clinical picture is complicated by factors associated with the moribund condition. A review of the actual clinical histories gives the impression that the quantity of the alloxuric bodies is dependent less on the number of leucocytes than on the severity of the disease as expressed in the clinical condition of the patient. Further, the view, at one time advanced by Nencki and Bieber, that the power of breaking down xanthin bodies to simpler substances is lessened in leuchæmia has been rudely shaken. Thus Bondzynski and Gottlieb (117) administered theobromine to a leuchæmic patient, and found that the theobromine taken *per os* was as completely decomposed in the organism of the leuchæmic patient as in that of a healthy individual. Schmid (120) also found, as the result of similar experiments, which he carried out with theobromine and caffeine, that the methyl groups are detached from these substances to the same extent in the leuchæmic as in the healthy organism. The theobromine taken had no influence on the excretion of uric acid; on the other hand, the quantity of the purin bases rose from 0·023 to 0·113 gramme after its administration. After the administration of caffeine the quantity of uric acid excreted rose from 0·368 to 0·485 gramme, and the quantity of purin bases was approximately double that found prior to the administration of the drug. Further, Galdi (103) administered on two different days two doses of 3 grammes of hypoxanthin to a case of myelogenous leuchæmia, with the result that a rise in the excretion of uric acid, as compared with that of the previous and of the succeeding day, was demonstrable in the first experiment, while in the second experiment the increase was only slight, amounting to little more than 0·1 gramme of uric acid. The quantity of xanthin bases excreted showed no distinct alteration in the first experiment, while in the second experiment it rose not inconsiderably both in the urine and in the fæces (about 100 milligrammes). Galdi reports a similar comparative investigation in which an excretion of uric acid amounting to 2·283 grammes was attained in one instance after the administration of 3 grammes of hypoxanthin, whereas the excretion on the two preceding days had amounted to 1·293 and 1·012 grammes. An experiment of the same nature had been previously carried out by Adrian in Naunyn's clinique. On the other hand, no distinct increase in uric acid followed the administration of thymus in the case of the patient examined by Adrian. The increase in the excretion of uric acid produced by the administration of thymus was also not greater in the case examined by Loewi (102) than in the normal individual.

O. Loewi sought in vain for allantoin in the case of a patient examined by him.

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Metabolism of the Salts.

(a) *Metabolism of Sodium Chloride.*

Kast (133) carried out experiments on the dog with reference to the effects produced by the withdrawal of blood upon the excretion of sodium chloride. He observed that the quantity of chlorine excreted per day sank from 0·46 to 0·057 gramme after the withdrawal of 200 c.c. of blood, and only reached its original level after six days. Markwald (134) made a similar observation in the case of man, and von Noorden (16) noted that only small quantities of chlorine (1·8 and 2·6 grammes) were present in the urine of two women two days after abortion accompanied by severe hæmorrhage, although the amount of food taken was not essentially diminished.

Different authors found in cases of chronic anæmia a fairly normal excretion of sodium chloride, which corresponded well with the amount present in the food (155, 71, 68, 56). Von Moraczewski alone maintains that a decrease in the excretion of chlorides in the urine is apparent as long as the diseased condition of the blood lasts, and that this decrease again ceases as the condition of the patient improves. Accurate investigations as regards the quantity of sodium chloride present in the food and fæces, however, are wanting in the first research of this author (99), while it is to be admitted that such estimations are present in his second research (136) dealing with the same subject. On the other hand, G. Vannini (75), as the result of experiments extending over five to six days, found in five cases of chlorosis a retention of chlorine in only one instance, while there was a loss of chlorine in the other cases.

In the case of pernicious anæmia, Schmidt (31) found at first an approximately normal condition in his Case I., while in Case II. " nothing abnormal " was noted. Unfortunately, accurate estimations of the NaCl present in the food and in the fæces are not given by Schmidt, or by Eichhorst (49) and Honigmann (56), who likewise did not observe any abnormal excretion of sodium chloride in pernicious anæmia. The first accurate investigations in this relation were made by von Stejskal and Erben (59), who noted a daily Cl retention of 0·77 gramme (= 1·27 NaCl) in an experiment extending over four days. A daily Cl retention of 0·0838 gramme = 0·124 gramme NaCl on a chlorine intake of approximately 1 gramme may be calculated in the Case I. investigated by Moraczewski (40) for a period of six days. The daily Cl retention in Case II. amounted to 0·296 gramme = 0·488 gramme of NaCl (duration of investigation two days), in Case III. it amounted to 0·715 gramme of chlorine = 1·117 grammes of NaCl (duration of investigation eleven days), and in Case IV. to 0·310 gramme = 0·511 gramme of NaCl. (It is to be noted that 10 grammes of calcium phosphate were given daily for a period of four days in Case III., and for a period of three days in Case IV.) I myself (60) found a daily NaCl retention of 1·6 grammes in a case of pernicious anæmia. The experiments extended over a period of ten days. Stejskal and R. Bernert (64) observed a daily NaCl loss of at least 3 grammes in their first case, while a retention of NaCl of more than

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1 gramme per day was noted in their second case. It appears to follow from these results that abnormal losses of NaCl form the exception rather than the rule in cases of anæmia, and retentions of NaCl, sometimes larger and sometimes smaller in amount, may be observed not at all infrequently. This fact is not entirely without interest, since, in addition to the experiments of Kast, which have already been mentioned, Kühnau (137) reported an increase in the NaCl excretion under the influence of the acute anæmia produced in the dog by the action of pyrogallol. Exact estimations of the sodium chloride present in the food and fæces are, however, wanting in these experiments.

Von Moraczewski (84), during a determination of nitrogenous equilibrium in cases of leuchæmia and pseudo-leuchæmia, found an excretion of Cl in the urine and fæces amounting to 5·61 grammes on a daily intake of chlorine amounting to 8·715 grammes (not 9·04 grammes, as the author states), so that a retention of chlorine amounting to 3·105 grammes (= 5·116 grammes of sodium chloride per day) was to be noted (eight days' experiment). The daily quantity of Cl absorbed in the case of pseudo-leuchæmia amounted to 10·085 grammes, and the amount excreted in the urine and fæces was 7·740 grammes. This result therefore corresponded to a daily retention of chlorine of 2·345 to 3·962 grammes of sodium chloride. Magnus-Levy (14) found in his case of acute leuchæmia that the quantity of chlorine excreted amounted to 10·14 grammes during the last forty hours of life, within which time the patient had taken 3½ litres of milk. The loss of chlorine was therefore considerable. Von Stejskal and Erben (87) found approximate equilibrium in the chlorine metabolism of a patient suffering from myelogenous leuchæmia, while they observed a retention of chlorine amounting to 4 grammes within four days in a case of lymphatic leuchæmia. The daily supply of chlorine amounted in both cases to barely more than 4 grammes (see also Nos. 45, 138, 182 in the literature).

(*b*) *Metabolism of Phosphoric Acid* (*including the Metabolism of Calcium and Magnesium*).

In the first place we may consider those estimations of the quantity of phosphoric acid present in the urine of anæmic and leuchæmic patients, in which the quantity of phosphoric acid excreted before and after a hæmorrhage by an individual on constant diet was investigated, or those in which a complete equilibrium was established in the metabolism of phosphoric acid. In an experiment which illustrates the first group, on the day of the blood-letting (150 c.c.) the excretion of P_2O_5 amounted to 3·21 grammes, while on the previous day it had amounted to 3·0 grammes. The average excretion for the three days preceding the withdrawal of blood was 2·78 grammes. In the case of patients suffering from chlorosis, von Moraczewski (136) found in three cases a retention on one occasion, and an increased excretion of phosphoric acid in two cases. Vannini (75) found the conditions variable in his five cases. Jacob and Bergell (90) found in one case of secondary posthæmorrhagic anæmia a retention of phosphoric acid amounting to 0·651 gramme per

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day as the result of an investigation extending over twelve days. In the case of "phthisis of the blood" which has already been mentioned, Kolisch and von Stejskal (67) found *sub finem vitæ* an excretion of phosphoric acid which on several occasions exceeded the intake to the extent of some grammes. Schmidt (31) observed a loss of phosphoric acid amounting to 8·705 grammes in four days in a case of pernicious anæmia, while in four similar cases von Moraczewski (40) found a retention of phosphoric acid. The quantity of phosphoric acid excreted approximately corresponded to that absorbed in the case of a patient examined by Stejskal and Erben (59). As the result of an investigation extending over ten days, I myself (60) noted in a case of pernicious anæmia a daily retention of phosphoric acid amounting to 1·29 grammes. Von Moraczewski (84) found a retention of phosphoric acid in myelogenous leuchæmia as well as in pseudo-leuchæmia, although to a less extent in the latter instance. On the other hand, von Stejskal and Erben (87) noted a slight increase in the quantity of phosphoric acid excreted amounting to 0·13 gramme per day in a case of myelogenous leuchæmia, while they noted a slight retention amounting to 0·22 gramme per day in a case of lymphatic leuchæmia. Magnus-Levy (14) observed in a case of acute leuchæmia *sub finem vitæ* a very considerable rise in the excretion of phosphoric acid. The quantity of phosphoric acid excreted by the patient during the last forty hours of life exceeded that absorbed by about 15 grammes.

The close relations subsisting on the one hand between the excretion of phosphoric acid and that of the earthy metals (calcium magnesium), and on the other between the excretion of phosphoric acid and that of nitrogenous substances, especially of uric acid, render it desirable to consider not only the metabolism of calcium oxide, but also the ratio, which the quantity of phosphoric acid excreted bears, both to the excretion of earthy metals and to that of the total nitrogen of the urine as well as to that of the uric acid (!).

Moraczewski (136) and Vannini (75) found in chlorotic cases sometimes a retention, sometimes an increased excretion of CaO. Vannini also draws attention to the presence of a relatively large amount of lime in the fæces of chlorotic individuals. Schmidt (31) found in a case of pernicious anæmia (Case I.), which he investigated during a period of four days, a total loss of calcium oxide amounting to 2·1166 grammes. In a case of pernicious anæmia, von Moraczewski (40) noted at different periods, sometimes a retention, at other times an increased excretion, at still other times equilibrium, but, as a rule, the loss of lime exceeded the gain. Schmidt (130) had already obtained similar results. Von Stejskal and Erben (59) noted within four days a total retention of 0·12 gramme of calcium oxide. Von Moraczewski (84) found in the case of myelogenous leuchæmia during the first period of his research a retention of lime, which became still more considerable after a more ample supply of lime salts (Period 5) had been given. Von Stejskal and Erben (87) found in their case of myelogenous leuchæmia that the intake and output of calcium oxide were approximately equal, while they observed in their case of lymphatic leuchæmia a total loss of calcium oxide amounting

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to 1·76 grammes in five days. In the case of pseudo-leuchæmia, von Moraczewski (84) found a daily retention of calcium oxide amounting to 0·641 gramme in a seven days' experiment.

Vannini (75) noted varying conditions with regard to the excretion of magnesium in his cases of chlorosis. Four of the five patients excreted more magnesium oxide in the fæces than in the urine. Schmidt (31) found approximate equilibrium in a case of pernicious anæmia. Von Stejskal and Erben have also found approximate equilibrium in a case of pernicious anæmia (59), as well as in a case of myelogenous and in one of lymphatic leuchæmia (87).

Setti (36) states that the ratio of the earthy phosphates to the alkaline phosphates is normal in chlorosis. Von Moraczewski (136) and Vannini (75) conclude from their figures that a certain decrease in the quantity of earthy phosphates takes place with a corresponding increase in the alkaline phosphates. In the case of "phthisis of the blood" examined by Kolisch and von Stejskal (67) the quantity of earthy phosphates varied between 0·45 and 0·798 gramme, and that of alkaline phosphates between 3·64 and 4·68 grammes. In Schmidt's (31) cases of pernicious anæmia the earthy phosphates amounted to about 12 per cent. (Case I.) and 4·87 per cent. (Case II.) of the total phosphates.

The ratio which the phosphoric acid bears to the calcium oxide has also been studied in connection with the question as to the source of the phosphoric acid excreted in the urine. Vannini (75) concluded from Moraczewski's (136) and his own figures that the phosphoric acid present in the urine of chlorotic patients is accompanied by so much calcium and magnesium and so little nitrogen that one may suspect a disintegration of osseous substance. In pernicious anæmia von Moraczewski (40) found in Case I. a slight increase in the quantity of phosphoric acid present in the urine as compared with that of the lime, in Case II. their relative proportion was fairly normal, and in Cases III. and IV. relatively more lime than phosphoric acid was excreted. On the other hand, the relative excess of phosphoric acid present in the case of "phthisis of the blood," investigated by Kolisch and von Stejskal (67), which has already been repeatedly referred to, favoured the view that the phosphoric acid is only to a very slight extent derived from the bones. A slight retention of lime was observable in von Stejskal and Erben's (59) case of pernicious anæmia, in which phosphoric acid equilibrium was maintained. Von Moraczewski (84) found the excretion of calcium oxide somewhat greater than that of phosphoric acid during the first period of investigation of a case of leuchæmia. On the other hand, the ratio was inverted in von Stejskal and Erben's (87) case of myelogenous leuchæmia, while the excretion of calcium oxide somewhat exceeded that of phosphoric acid in the case of lymphatic leuchæmia examined by the same authors. In the case of acute leuchæmia examined by Magnus-Levy (14), the excretion of phosphoric acid as compared with that of calcium and magnesium oxides was considerably greater than the ratio of the phosphoric acid to the calcium and magnesium oxides of the food.

The foregoing results are in many respects conflicting. If those cases of chlorosis are neglected in which the factors involved are not so readily

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accessible to review, the results obtained only slightly favour the view that the rise in the excretion of phosphoric acid occasionally observed in severe cases of disease of the blood is to be referred to a destruction of osseous tissue. The impression rather obtains that the rise in the excretion of phosphoric acid observed in severe cases of anæmia and leuchæmia is to be referred to the decomposition of nitrogenous substances, especially those containing a nuclein radicle. Critical consideration of the quotients $\frac{N}{P_2O_5}$ and $\frac{\text{Uric Acid}}{P_2O_5}$ to some extent favours such a theory. The first of these quotients amounts to an average value of 5 [W. Zülzer (140)], while the second, on a comprehensive review of different investigations on healthy individuals, is found to amount to about 0·33.

A calculation of the quotient $\frac{N}{P_2O_5}$ from cases in the earlier literature of the subject is to be found in the work of von Noorden (16). As the result of this calculation, the ratio which the nitrogen bears to the P_2O_5 was found not to deviate essentially from the average. On the other hand, patients suffering from advanced anæmia excreted strikingly large quantities of phosphoric acid. The material available for the critical consideration of the quotients $\frac{N}{P_2O_5}$ and $\frac{\text{Uric Acid}}{P_2O_5}$, which has accumulated since that time, deals mainly with cases of pernicious anæmia and leuchæmia. Investigations on other forms of disease of the blood are comparatively few in number. Thus Vannini (75) found in cases of chlorosis values for $\frac{N}{P_2O_5}$ which varied from 5·64 to 8·48. Jacob and Bergell (90) noted in the case of chlorosis $\frac{N}{P_2O_5} = 5·2$ (average of eleven days), and in secondary posthæmorrhagic anæmia the following quotients: $\frac{N}{P_2O_5} = 5·1$, $\frac{\text{Uric Acid}}{P_2O_5} = 0·44$ (average of seven days in Case I.); and in Case III., $\frac{N}{P_2O_5} = 8·0$ and $\frac{\text{Uric Acid}}{P_2O_5} = 0·34$ (average of five days). The following tables show the results of investigations on cases of pernicious anæmia and leuchæmia:

A.—PERNICIOUS ANÆMIA.

Author.	*Nitrogen.*	*Uric Acid.*
	P_2O_5.	P_2O_5.
Brandenburg (three days)	7·7	0·50
Von Stejskal and Kolisch (two days)	5·1	—
R. Schmidt, Case I. (eleven and nine days respectively) ..	8·4	0·49
R. Schmidt, Case II. (three days)	5·2	0·28
Jacob and Bergell (six days)	5·8	0·41

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Author.	Nitrogen.	Uric Acid.
	P_2O_5.	P_2O_4.
Taylor	5·8	0·33
White and Hopkins	5·4	—
Von Stejskal and Erben (four days)	3·2	0·23
H. Strauss (ten days)	6·6	0·52
Rosenqvist, Case IV.	4·3	0·10
,, ,, VI.	8·4	0·20
,, ,, VII.	6·1	0·31
,, ,, XI. (nine days)	5·1	0·24
,, ,, XII. (seven days)	6·1	0·18
,, ,, XIII. (eight days)	6·6	0·31
,, ,, XIV. (eight days)	6·5	0·47
,, ,, XVII. (ten days)	4·1	0·23
,, ,, XX. (sixteen days)	4·3	0·32
,, ,, XXI. (nine days)	4·3	0·40
,, ,, XXII., metabolism of V. (three days)	3·4	0·30

B.—LEUCHÆMIA.

Author.	Nitrogen.	Uric Acid.
	P_2O_5.	P_2O_4.
In the myelogenous form the following results were obtained:		
Taylor, in Case I.	6·6	0·72
Taylor, in Case III.	8·6	0·43
Milroy and Malcolm	9·2	0·66
White and Hopkins (four days)	8·6	0·80
O. Loewi (thirteen days)	7·9	0·67
Von Stejskal and Erben (five days)	4·9	0·28
Kaufmann and Mohr, in Case I. (six days), on a diet free from purin bodies	5·3	0·37
Kaufmann and Mohr, in Case II. (four days)	5·1	0·34
Schmidt (July 2 to 11)	7·8	0·86
In the lymphatic form the following result was obtained:		
Von Stejskal and Erben	3·6	0·22

Magnus-Levy found in a case of acute leuchæmia the quotient $\frac{N}{P_2O_5}$ = 2·62 and $\frac{\text{Uric Acid}}{P_2O_5}$ = 0·80 during the last two days of life. In Ebstein's case the quotient $\frac{N}{P_2O_5}$ was equal to 4·1.

In a case of acute leuchæmia, the urine contained 29·534 grammes nitrogen and 3·056 grammes P_2O_5; while the food contained only 7·25 grammes nitrogen and 1·849 grammes P_2O_5 (Edsall, *A. J. M. S.*, 1905, October).

With the exception of one case of pernicious anæmia examined by

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von Stejskal and Erben, and of one case of Magnus-Levy examined *sub finem vitæ*, the quotient $\frac{N}{P_2O_5}$ was always either nearly 5 or equal to 5, or greater than 5. A strikingly large excretion of phosphoric acid as compared with that of nitrogen only occurred in a relatively small number of cases, and in many cases a direct retention of phosphoric acid appears to have taken place.

Specially low values for the quotient $\frac{\text{Uric Acid}}{P_2O_5}$ were found only in some of Rosenqvist's cases, as well as in von Stejskal and Erben's case of lymphatic leuchæmia. In those cases in which the value for the quotient $\frac{\text{Uric Acid}}{P_2O_5}$ lay below 0·2, this result was usually due to an abnormal decrease in the absolute values for the excretion of uric acid, and only rarely due to a rise in the values for phosphoric acid.

Compared with the amount of uric acid excreted, often only relatively small quantities of phosphoric acid appear in the urine. The abnormally high absolute values for the excretion of phosphoric acid were usually only observed in very severe cases, and, as a rule, only towards the close of life. The organism, therefore, appears to deal with phosphoric acid on strictly economical principles, utilizing anew for the reconstruction of cellular elements the phosphoric acid set free by the breaking down of other cells within the organism. Larger quantities of phosphoric acid only appear in the urine in those cases in which regenerative processes are deficient. Kühnau's (137) experiments may also be interpreted as signifying that the phosphoric acid set free as a result of cellular katabolism is again utilized by the organism. He observed that the quantity of phosphoric acid excreted by dogs rose in the first days after poisoning with pyrogallol, while later on the quantity excreted was diminished. The foregoing experiments by Kühnau possess still farther interest, inasmuch as a certain antagonism is observable in them between the excretion of sodium chloride and that of phosphoric acid of such a nature that when the quantity of sodium chloride is large that of phosphoric acid is small, and *vice versa*. Von Moraczewski also lays stress on the value of a comparative consideration of the quantities of sodium chloride and phosphoric acid simultaneously excreted. Whereas Kühnau noted in his experiments on animals that the excretion of sodium chloride frequently rose more markedly than that of phosphoric acid, von Moraczewski, on the other hand, frequently observed in pernicious anæmia a converse condition, which not infrequently led to a retention of sodium chloride. The latter author was also able to establish a smaller retention of sodium chloride in cases of chlorosis. In Cario's (138) case of leuchæmia the quantity of phosphoric acid (7 grammes) amounted to double that of the sodium chloride (3·45 grammes).

Vannini's (75) figures show that a slight loss in Na_2O and K_2O is more frequent in chlorosis than a slight retention of these substances.

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III.—THE INFLUENCE OF DISEASES OF THE BLOOD UPON THE PHYSICAL AND CHEMICAL CHARACTERS OF THE URINE.

1. Quantity, Specific Gravity, and Lowering of the Freezing-point of Urine.

The quantity of the urine is usually found to be normal and not infrequently increased in uncomplicated cases of anæmia, whatever the type. The rise in the quantity of urine ranges, as a rule, only within moderate or average limits, or periods in which the quantity is normal alternate with periods of polyuria. A diminution in the quantity of urine may usually be regarded as due to cardiac or renal complications.

The specific gravity of the urine also usually varies within normal limits in uncomplicated cases, and shows, as a rule, only slight variations upward or downward.

According to von Koranyi (63), as well as my own observations,[1] the lowering of the freezing-point produced by urine is frequently less than normal. Hyposthenuria is therefore frequently present, and not infrequently a direct molecular oliguria. I myself have found that the "equivalent number" in different forms of anæmia lay relatively frequently in the neighbourhood of 1,000 to 1,200, consequently nearer the lower than the upper limit. This fact appears to indicate a certain tendency to polyhydruria. The quotient $\frac{\Delta}{NaCl}$ is generally subject to greater variation in anæmic than in healthy individuals. These disturbances may be regarded as a sign of instability in renal activity due to the anæmia. It is, indeed, also known that anatomical alterations may sometimes be detected in the kidneys both by macroscopic and microscopic methods in cases of severe disease of the blood, especially in leuchæmic conditions.

2. Colour and Reaction of the Urine.

The colour of the urine is chiefly of interest in diseases of the blood in connection with the amount of urobilin present in it, since this affords a certain indication for determining the extent of the decomposition of hæmoglobin. Yet the use of the estimation of the urobilin present in the urine as a diagnostic test requires a certain limitation even in

[1] The terms used by the author in this paragraph may be defined as follows:

When the depression of the freezing-point of urine varies from $-0{\cdot}56°$ to $-1{\cdot}3°$ (normal depression, $-1{\cdot}3°$ to $-2{\cdot}2°$), the condition is termed "hyposthenuria" [Koranyi]. When the substances dissolved in urine are expressed in terms of a sodium chloride solution producing the same depression of the freezing-point, the latter expression is termed the sodium chloride equivalent. This equivalent is calculated from the formula $\frac{\Delta K}{0{\cdot}613}$ (Δ = depression, K = twenty-four hours' urine in decilitres, and $0{\cdot}613 = \Delta$ produced by 1 per cent. NaCl).

The sodium chloride equivalent normally amounts to 30 to 40. If it continue below 30, the condition is termed "molecular oliguria" [Koranyi]. Strauss names the product of the quantity of the urine (twenty-four hours) multiplied by Δ the equivalent number [Valenzzahl]. (*Cf.* Koranyi, *Zeitschr. f. Klin. Med.*, vols. xxxiii. and xxxiv.; and Strauss, vol. xlvii.)

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this connection. As a rule, it may be taken that the urine is clear or even pale in cases of chlorosis. An increased amount of pigment can sometimes be observed, but only in cases in which the chlorosis is running a rapid course, or in cases in which complications are present. The urine shows a variable depth of colour in leuchæmia. The colour is sometimes normal, at other times paler than normal, and in other instances deeper than normal.

On the other hand, the urine is frequently found to be more deeply coloured than normal in pernicious anæmia, even when its quantity is not diminished. In such cases an increase in the quantity of urobilin is frequently demonstrable with the aid of the qualitative reaction (31, 39, 60, 141). It is interesting to note that Weintraud (124D) found only a small amount of urobilin in the urine of a case of poliocythæmia associated with enlargement of the spleen. Quantitative estimations of urobilin have been carried out by Hoppe-Seyler (142) in the case of chlorosis and by von Noorden (76). In five cases of severe chlorosis von Noorden found 0·03 to 0·124 gramme excreted per day, and Hoppe-Seyler traces up to a maximum of 0·019 gramme per day. These are values which appear low in comparison with the average daily quantity of 0·123 gramme determined by Hoppe-Seyler in the case of healthy individuals. The fæces contained 0·021 to 0·029 gramme of urobilin in two of von Noorden's cases. Garrod (143) also was unable to find any rise in the excretion of urobilin in cases of chlorosis. Hoppe-Seyler (142) found 0·107 gramme per day in the urine of a case of pernicious anæmia, and 0·11 gramme per day in cases of pseudo-leuchæmia and leuchæmia. Von Noorden (76) found an excretion of urobilin amounting to 0·153 gramme per day in a case of pernicious anæmia. This patient excreted a quantity amounting to 0·92 gramme per day in the fæces.

On the whole, it may be concluded from a general review embracing the results of the qualitative and quantitative examination of the urine for urobilin, that these results are not opposed to the theory that an increased decomposition of hæmoglobin occurs in the case of pernicious anæmia, and that such an increased destruction is highly improbable in the case of chlorosis. It should also be added that Taylor (39) found a larger quantity of hæmatoporphyrin than normal in a case of pernicious anæmia, and that Schmidt (31) gives a report of an observation on pernicious anæmia in which hæmoglobinuria was present for some time.

The reaction of the urine is usually acid, or at least neutral, in the different forms of anæmia. With the aid of Freund and Töpfer's method, Schmidt (31) examined the acidity and alkalinity in two cases of pernicious anæmia. He found that the acidity determined for the quantity of urine excreted during the twenty-four hours corresponded to an amount of hydrochloric acid varying from 0 to 2·610 grammes, and that the alkalinity expressed in terms of caustic soda corresponded to 0·616 to 2·52 grammes. In Case II. the average acidity for three days corresponded to 2·47 grammes of hydrochloric acid, and the alkalinity to 1·24 grammes NaOH. I have observed a degree of acidity (average of ten days) amounting to 50·9 per cent. in the case of pernicious anæmia (Freund and Lieblein's method). The acidity in this case varied from

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42 to 60 per cent. If the variations observed by R. Schmidt in Case I. be neglected, these figures may be looked upon as representing conditions which closely approximate to the normal.

3. Relative Proportions of the Different Constituents contributing to the Total Nitrogen of the Urine.

As regards the distribution of the nitrogenous constituents, the quantity of urea and that of ammonia are of primary interest. The so-called precipitable nitrogen, which is obtained on the addition of hydrochloric acid and phosphotungstic acid to the urine, and the nitrogen derived from amino-acids come next in importance. In consequence of the altered views with regard to the part played by uric acid in nitrogenous metabolism, the relation of uric acid to the total nitrogen no longer possesses the same interest as formerly. For this reason, as well as on account of the fact that the problems involved in the metabolism of uric acid have been already discussed, we shall here leave uric acid out of account.

(*a*) *Urea.*

Under the direction of von Noorden, Voges (92) and Friedrichsen (98) found in chlorosis an approximately normal value (namely, 83 to 85 per cent.) in two out of a total of seven analyses, while the values were higher in the remaining cases, varying from 87 to 93 per cent. P. Chatin (144) found 83 to 86 per cent. in four instances, and 87 to 90 per cent. in six instances. Voges (92) found in two cases of severe anæmia resulting from gastric hæmorrhage values which varied from 80·1 to 89·2 per cent., while he found only 72·4 per cent. in another very severe case (Case F) on the day of the patient's death (state of collapse). Halpern (100) found by means of Schöndorff's method 87·39 per cent. (average of three days) in a case of severe secondary anæmia.

Von Noorden noted a marked reduction in the percentage of urea nitrogen in some cases of pernicious anæmia—67·9 to 74·0 per cent. of the total nitrogen were excreted in the form of urea in cases of advanced disease; the condition was complicated in both cases by severe œdema. Voges frequently found normal conditions, but in some instances the percentage of urea nitrogen was lowered. Taylor (39) found 83·6 per cent. in one instance. Schmidt (31), using Sjöqvist's method, found 83·9 per cent. (average of ten days) in Case I., and 88·5 per cent. of urea nitrogen (average of three days) in Case II. The nitrogen excreted in the form of urea amounted to about 85 per cent. in von Stejskal and Erben's case. Von Jaksch (66) found 86·53 per cent. of urea nitrogen in a case of anæmia due to anchylostomiasis (Schöndorff's method). Halpern (100) found an average value of 84·49 per cent. (average of three days) in a case of anæmia splenica. The urea nitrogen varied from 86·1 to 91·3 per cent. in a similar case examined by Umber (62A), while the quantity of nitrogen present in the total filtrate from the precipitate produced by phosphotungstic and hydrochloric acids varied from 89·8 to 94·2 per cent. in the second case.

Von Noorden found 83 to 86 per cent. of urea nitrogen in chronic

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myelogenous leuchæmia as well as in lymphatic leuchæmia. Taylor, using the method of Mörner and Sjöqvist, noted 80·7 per cent. on one occasion, 80·2 per cent. of urea nitrogen in another instance. Von Jaksch (66) found 92·08 per cent. in a case of myelogenous leuchæmia, and 83·41 per cent. in another case. Halpern (100) found 87 to 73 per cent. (average of five days) in a case of lymphatic leuchæmia.

(*b*) *Ammonia.*

After the withdrawal of blood from the human subject I myself found, as the result of three investigations, that the quantity of ammonia excreted was approximately the same both before and after the blood-letting. Voges (92) observed that the quantity of ammonia nitrogen varied from 2·9 to 11·4 per cent. in cases of severe anæmia following gastric hæmorrhage. Halpern (100) found 3·1 per cent. of nitrogen excreted as ammonia in a case of severe secondary anæmia. I myself noted values for the excretion of ammonia after severe gastric hæmorrhage varying from 0·747 to 0·970 gramme. In these cases the quantity of nitrogen excreted as ammonia amounted to 3·6 to 6·1 per cent. of the total nitrogen. The latter values, however, were only found in the days immediately succeeding the hæmorrhage, and on the following days they lay within the physiological limits, which, as is well known, are represented by an excretion amounting to 2 to 5 per cent. of the total nitrogen. Voges (92) and Friedrichsen (98) found 4·9 to 8·1 per cent. of nitrogen excreted in the form of ammonia—that is, somewhat high values.

In pernicious anæmia Voges obtained numerical results which varied from 2·1 to 9 per cent. Taylor (39) noted a value of 5·87 per cent. In the latter case the total average daily quantity excreted was 0·42 gramme. Schmidt (31) found a value of 3·99 per cent. (average of nine days) in his first case, the corresponding average daily excretion being 0·444 gramme; and a value of 2·1 per cent. in his second case, with a corresponding average daily excretion amounting to 0·305 gramme. Von Moraczewski (40) noted a relative increase in the quantity of ammonia excreted, which also continued after the administration of lime. The quantity of nitrogen excreted in the form of ammonia amounted to 8·1 per cent. in von Stejskal and Erben's case, while the corresponding total average daily excretion (average of three days) was 0·553 gramme. I myself found in one case a value of 5·4 per cent. (average of ten days' observations), the corresponding average amount excreted per day being 0·728 gramme. In a second case I found a value of 4·4 per cent. (average of four days), the corresponding daily excretion being 0·501 gramme; and in a third case I found a value of 4·4 per cent. (average of three days), the corresponding average daily excretion being 0·385 gramme. Halpern (100) found that the nitrogen excreted as ammonia formed 5·45 per cent. of the total nitrogen in a case of anæmia splenica. The actual average quantity of nitrogen excreted per day as ammonia was 0·54 gramme in this case. Umber (62A) found values for the nitrogen excreted in the form of ammonia varying from 0·352 to 0·84 gramme in a case of toxic anæmia of splenic origin.

In leuchæmia Hallervorden (145) estimated the daily amount as

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0·13 to 0·59 gramme. The nitrogen excreted in the form of ammonia varied from 0·365 to 0·6 gramme in a case examined by Stadelmann (146). Bondzynski and R. Gottlieb (117) found the high value of 1·224 grammes of nitrogen excreted as ammonia (average of two days). Taylor noted 3·01 per cent. in his first case (daily amount 0·616 gramme), and 3·2 per cent. in his second case (daily amount 0·703 gramme). In three cases of acute leuchæmia, Magnus-Levy (14) found an average value of 2·5 per cent. in one instance, and of 4·4 per cent. in two instances. The total quantities excreted daily amounted to 0·992 gramme (average of two days), to 0·93 gramme (average of eleven days), and to 0·90 gramme (average of seven days' observations). The value for the last twenty days of life amounted to 8·3 per cent. in a case of chronic leuchæmia (average daily amount 0·57 gramme). Von Stejskal and Erben (87) noted 3·6 per cent. in a case of myelogenous leuchæmia. The average amount excreted per day amounted to 0·67 gramme (average of five days) in this case. The corresponding figures for a case of lymphatic leuchæmia were 6·43 per cent. and 0·77 gramme for the ammonia nitrogen. The corresponding figure was 0·396 gramme (average of three days) in a case of pseudo-leuchæmia [Moraczewski (84)]. I myself found 0·488 gramme of ammonia nitrogen (average of three days) in a case of pseudo-leuchæmia. Halpern found 0·739 gramme of ammonia and 4·94 per cent. of ammonia nitrogen in lymphatic leuchæmia.

(c) *Other Nitrogenous Products of Protein Decomposition (Amino-Acids, Ptomaines, etc.).*

Halpern (100) estimated the proportion of the total urinary nitrogen precipitable by phosphotungstic acid plus hydrochloric acid in a case of severe secondary anæmia. He found 8·69 per cent. as the average of observations extending over three days. In a case of anæmia splenica 12·37 per cent. was the average of three days. Umber (62A) found values varying from 6·5 to 10·4 per cent. in the case of a patient maintained on a diet free from purin bodies. This case has already been frequently referred to. Von Jaksch found values amounting to 6·55, 6·2, and 6·66 per cent. in anæmia due to anchylostomiasis. He noted values varying from 2·83 to 6·09 per cent. as the result of four observations in cases of myelogenous leuchæmia. Consequently the average amount excreted by the normal individual, which is stated by A. Landau (147) to be 6·24 per cent. (maximum 7·53 per cent.), is only sometimes exceeded in diseases of the blood.

Halpern (100) has further calculated the quantity of these nitrogenous constituents of the precipitate produced by phosphotungstic acid which are not represented by purin bodies or ammonia, and has named this value, the chief constituents in which are creatinin, carbaminic acid, diamines, thiocyanates, certain nitrogenous pigments, and chromogens, "the nitrogen of the extractives." Halpern found a value of 5·26 per cent. for this group in a case of severe secondary anæmia as well as in a case of splenic anæmia. The corresponding value was 2·76 per cent. in a case of lymphatic leuchæmia.

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Von Jaksch (66), Halpern (100), and Umber (62A) have carried out investigations dealing with the nitrogen of the amino-acids which, as is well known, indicates the quantity of oxyproteic acid, hippuric acid, leucin, tyrosin, cystin, creatinin, etc., present in the urine.[1] Von Jaksch found a value of 2·28 per cent. in one case of anæmia due to anchylostoma, and values varying from 1·58 to 2·83 per cent. in two cases of myelogenic leuchæmia. Halpern found 2·74 per cent. in a case of severe secondary anæmia, 2·23 per cent. in a case of anæmia splenica, and 2·58 per cent. of nitrogen derived from amino-acids in a case of lymphatic leuchæmia. These are values which cannot be regarded as high if one takes into consideration the facts that M. Pfaundler (148) found 4·76 per cent. and M. Krüger and P. Schmidt (149) 2·5 to 6 per cent. of the total nitrogen excreted on a mixed diet in the form of amino-acids. The total quantity of the nitrogen derived from amino-acids amounted to an average of 0·2148 gramme (0·11 to 0·37 gramme) in von Jaksch's cases, and to 0·328 gramme (0·184 to 0·487 gramme) in Halpern's cases. The nitrogen derived from amino-acids varied from 1·4 to 6·9 per cent. of the total nitrogen in Umber's case of "toxic anæmia of splenic origin."

Von Noorden (16) has never succeeded in finding leucin and tyrosin even in severe forms of chlorosis and traumatic anæmia. H. Müller (51) and Laache (55) have occasionally found in cases of pernicious anæmia crystals which showed a great similarity to leucin spherules. Von Noorden also made a similar observation on one occasion, yet the crystals referred to did not yield the indispensable test of Scherer. Laache (55) found tyrosin on three occasions, and von Noorden (16) twice *sub finem vitæ*. Von Noorden failed to obtain this result in five other cases. Taylor (39) states that he has searched in vain for leucin, tyrosin, and cystin. Taylor also makes the same statement with regard to two cases of myelogenous leuchæmia.

K. B. Hoffmann (150) found 0·593 to 0·604 gramme per day of creatinin in chlorosis. Von Stejskal and Erben (59) found on one occasion 0·23 gramme in a case of pernicious anæmia. They found an average excretion of 0·348 gramme in myelogenous leuchæmia, and of 0·018 gramme in lymphatic leuchæmia. Von Moraczewski (84) found an average daily value of 0·390 gramme in pseudo-leuchæmia. These are, on the whole, low results.

Von Moraczewski reports the presence of creatin in a case of myelogenous leuchæmia in an amount which only rarely reached 0·05 gramme.

Taylor (39) has vainly sought for ptomaines in pernicious anæmia and in myelogenous leuchæmia. Bloch (61) states that he sometimes succeeded in separating alkaloidal compounds in Biermer's anæmia by means of Griffith's method. The quantities were, however, usually too small to allow him to undertake extensive investigations of the products obtained. Bloch was able to separate on one occasion a diamine by means of Baumann and Udransky's benzoyl method, yet the patient examined in this case suffered from a concurrent catarrh of the urinary bladder.

[1] The excretion of the amino-acids in diseases of the blood requires further investigation with the aid of Emil Fischer's methods for their separation, especially that of precipitation as compounds with β-naphthalene sulphonic chloride (*cf.* Fischer, "Untersuch. über Amino-säuren, Polypeptide und Proteïne," pp. 196-204; also Amino-Acids, Vol. I.).

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4. Other Products of Decomposition of Protein.

The following products have a special interest:

(*a*) *Indican and Phenol.*

Since H. Senator (167) studied the excretion of indican in chlorosis, leuchæmia, and pseudo-leuchæmia, as well as in the different forms of anæmia, including pernicious anæmia, and succeeded in determining an increase in urinary indican in pernicious anæmia, the amount of indican present in the urine in different forms of anæmia has been made the subject of numerous investigations (168, 169, 170, 171, 172). The result of these investigations was that an increase in the quantity of indican present in the urine could be demonstrated with a certain frequency almost only in cases of pernicious anæmia. Even under these conditions it was neither observable in all cases, nor throughout the whole course of the disease in those cases in which its presence had been detected. Within the last two years Strauss has investigated the excretion of indican in three cases of chlorosis, two cases of pernicious anæmia, and one case of anæmia splenica by means of his quantitative method. The result obtained was usually less than 2·5 milligrammes per day in cases of chlorosis (normal excretion 2 to 4 milligrammes per day). The values varied from 8 to 32 milligrammes per day in severe secondary anæmia resulting from recurrent gastric hæmorrhage, continuing at this level as long as the fæces contained chemically demonstrable quantities of blood. The results varied from traces up to 12·3 milligrammes per day in anæmia splenica. The results obtained in anæmia gravis were found to vary from barely measurable traces up to 4·1 milligrammes per day. Since I noted a considerable fall in the quantity excreted by a case of pernicious anæmia as the result of the administration of a milk diet, the theory that the quantity of indican excreted is, *ceteris paribus*, more dependent upon the extent of the intestinal putrefactive processes than upon the anæmia in itself appears to me a justifiable one in view of the similar experimental results obtained in the case of healthy individuals by myself and other observers. At any rate, without further evidence I cannot induce myself to agree with the hypothesis that a formation of indican occurs as a result of tissue change [F. Blumenthal (34), G. Rosenfeld (174A), C. Lewin (174B)]; although, as I have elsewhere made clear, I readily agree that the transforming activity of the tissues may be so injuriously affected by severe disturbances of nutrition that less indican is transformed into other compounds than under normal conditions. In those cases in which there is a possibility of the extravasation of blood into the alimentary canal, I am inclined to regard putrefactive changes in the extravasated blood as the chief source of the increased excretion of indican. I have been led to form this conclusion, which agrees with that of M. Jaffé (174D), as the result of investigations carried out by myself, and by Koziczkowski (174A) at my suggestion. Eckert (1C) noted that the increase in the excretion of indican occurring in anæmia due to bothriocephalus ceased after evacuation of the worms. Brieger (175) found large quantities of indican in severe anæmia, but only traces in chlorosis.

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Brieger (1c) also found mere traces of phenol in severe types of anæmia, and I have also found the excretion of phenol increased in a case of pernicious anæmia.

(*b*) *The Ethereal Sulphates* (*including the Total Sulphuric Acid*).

A discussion of this problem opens up the whole question of the excretion of sulphuric acid. In this connection it is recognised by all that the total sulphuric acid, the so-called preformed sulphuric acid, and the ethereal compounds of sulphuric acid, are to be distinguished from one another. The majority of the estimations which have found a place in the literature of the subject deal with the ethereal compounds of sulphuric acid, yet, as the following table shows, some authors have also directed more or less attention to the other forms in which sulphuric acid may be excreted. Von Moraczewski (40) has studied in several investigations the total quantity of sulphur excreted in pernicious anæmia. He took into consideration the amount of sulphur absorbed and that present in the fæces of each case. He found, as a result of this investigation, in some instances a small loss, in others a slight retention of sulphur. Vannini (75) found in three out of four cases of chlorosis a slight retention of sulphur, and in one instance a slight loss. The total quantity of sulphuric acid present in the urine was approximately proportional to the amount of nitrogen excreted in the experiments on the total excretion of sulphuric acid in anæmia gravis and leuchæmia, which were carried out by von Stejskal and Erben (59 and 87), Taylor (39), Schmidt (31), von Moraczewski (40, 84).

Rethers (176), working under the direction of von Noorden, found in nine out of eighteen cases of chlorosis—*i.e.*, in half the cases—values for the excretion of the ethereal compounds of sulphuric acid which were less than 0·2 gramme. Von Noorden (76) observed in the urine of four chlorotic girls average values for three days amounting to 0·17, 0·19, 0·25, and 0·26 gramme of ethereal sulphates. Conti and Vitale (177) were also unable to demonstrate an increased excretion of aromatic substances in chlorosis. Vannini's results (75), giving the quantities of ethereal sulphates excreted in five cases of chlorosis, were likewise low (0·12 to 0·15 gramme. In the case of anæmia due to helminthes, Vannini (65A) (anæmia due to anchylostoma) and Eckert (172) found a rise in the excretion of ethereal sulphates, which, in the cases of the latter author, was succeeded by a fall after the evacuation of the worm. As the result of an investigation extending over nine days, Schmidt (31) found a relatively low excretion (0·136 gramme) in Case I. of the cryptogenetic type of pernicious anæmia, while Case II. showed a fairly normal excretion (0·250 gramme; period of observation, three days). The values which von Moraczewski obtained in two cases were strikingly low, for the average amount excreted per day amounted to only 0·029 gramme (average of eight days) in Case II., and to 0·028 gramme (average of seven days) in Case III. The results obtained in two of my own cases were fairly normal [Case I., 0·216 gramme (average of ten days), and Case II., 0·169 gramme (average of four days)].

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In contrast to the foregoing results, Meyer's (175) earlier investigations frequently indicated the occurrence of an increase in the quantity of sulphuric acid excreted in cases of severe anæmia. On reviewing all these results, a low or normal value for the excretion so frequently obtains that an increased excretion, such as that observed by Taylor (39), must be considered as exceptional in cases of pernicious anæmia. The occurrence of very considerable variations becomes at once apparent on reviewing Schmidt's series of observations (nine days), and the similar series (ten days) of investigations carried out by myself. Thus, for example, the minimal value given by Schmidt amounted to 0·072 gramme, and the maximal to 0·201 gramme. The minimal value in my own researches amounted to 1·168 grammes, while the maximal value was 0·299 gramme.

Taylor (39) found an average value of 0·34 gramme in two cases of leuchæmia.

The following table gives the main chemical data :

Author.	*Duration of Investigations.*	*Total Nitrogen.*	*Total H_2SO_4.*	*Preformed H_2SO_4.*	*Ethereal Sulphuric Acid.*	*Neutral Sulphur.*
PERNICIOUS ANÆMIA :						
R. Schmidt ..	Nine days	14·75	2·759	2·423	0·136	0·731
,, ..	Three days	16·22	3·558	1·897	0·250	1·162
Taylor	—	7·15	2·066	1·221	0·704	0·141
Von Moraczewski	Eight days	7·802	0·614	0·451	0·029	0·129
,, ..	Seven days	6·192	0·491	0·407	0·028	0·056
H. Strauss ..	Ten days	13·37	2·042	—	0·216	—
LEUCHÆMIA :						
Taylor	—	20·413	3·862	3·028	0·339	0·495
,, ...	—	18·06	2·435	1·557	0·354	0·524

(c) *The Toxicity of the Urine.*

Notwithstanding the great defects associated with Bouchard's method for testing urinary toxicity by means of experiments on animals, some results of such investigations may here be given. Thus Picchini and Conti (185) found that the toxicity of the urine was greater in chlorosis when the disease was at its height than after recovery. On the other hand, P. Chatin (145) found a diminution of the urotoxic coefficient during the course of the disease. Forchheimer (186) found that the substances precipitable by alcohol which were present in the urine of chlorotic patients proved poisonous to rabbits. Similar experiments were also carried out in the case of anæmia due to anchylostoma. Lussana (187) injected an alcoholic extract of the urine of a patient suffering from anchylostomiasis into rabbits, and stated that he produced by this means the following results : a diminution in the number of erythrocytes, the appearance of poikilocytes, a diminution in the quantity of fibrin as well as in the affinity shown by the corpuscular elements for histological stains. Arslan (188) obtained from the urine of two children

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suffering from anæmia due to anchylostoma a substance which, on injection, caused a diminution of hæmoglobin and a reduction in the number of erythrocytes in rabbits' blood. Yet Crisafulli (189) and, later on, Aporti (190) were able to produce an exactly similar action on injection of an extract obtained from the urine of a healthy individual, as well as from that excreted by a patient suffering from chronic intestinal catarrh. Vannini observed a rise of the urotoxic coefficient in anæmia due to anchylostoma. He noted at the height of the disease values up to 0·88, which, after treatment, gradually diminished to 0·422. I myself have found a low urotoxic coefficient in a case belonging to the cryptogenetic type of pernicious anæmia. The precipitate produced by alcohol, as well as the filtrate, showed only a slight toxic action on injection into the vein of a rabbit. Bloch (61) was also able to obtain the like effects as the result of similar experiments. Consequently, the view that the urine shows a heightened toxicity in severe cases of anæmia cannot be regarded as proved.

5. The Iron contained in the Urine.

The amount of iron contained in the urine in diseases of the blood was studied by Hunter (178), Damaskin (179), Hopkins (180), Jolles and F. Winkler (181), as well as by A. Mayer (182). Hunter states that the amount of iron excreted in the urine of a patient suffering from pernicious anæmia, whose urine was examined for a period of two and a half months, rose from 2 to 3 milligrammes up to 22 milligrammes per day. Damaskin found that the quantity of iron excreted daily in a case of traumatic anæmia amounted to 0·57 to 0·76 milligramme, while he was able to determine a daily excretion of iron amounting to 3·08 milligrammes in a case of pernicious anæmia as contrasted with the normal excretion of 1 milligramme. Hopkins found, in a case of pernicious anæmia, 8·3 milligrammes on one day, while shortly afterwards only traces of iron were present. Mayer, who employed Neumann's method, found values varying from 1·047 to 2·723 milligrammes in five cases of chlorosis, and values of 1·549 and 2·154 milligrammes in two cases of anæmia. Neumann and Mayer (183) had found, using the same method, that the average quantity excreted by a healthy individual was 0·983 milligramme. Jolles and Winkler found, by means of a volumetric method (reduction of the iron solution with zinc, and titration with potassium permanganate), that the average amount excreted daily by a healthy adult was 8·0 milligrammes, while the quantities excreted in two cases of chlorosis were 6·8 and 7·7 milligrammes, and the excretion varied from 28·0 to 52·7 milligrammes in four cases of anæmia gravis. They found that 14·3 milligrammes were excreted per day in a case of leuchæmia. In consideration of these values, one may well agree with F. Kraus (184) in expressing the view that the little one knows concerning the metabolism of iron is not opposed to the hypothesis that a deficient formation of hæmoglobin may be assumed to occur in chlorosis, and that an increased decomposition of hæmoglobin is a characteristic feature of pernicious anæmia.

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6. Protein and Allied Constituents of the Urine.

Native albumin may be present in the urine in cases of severe anæmia of the most varying kind, partly as a consequence of malnutrition of the kidneys, partly owing to local anatomical alterations occurring as complications of the disease. Febrile conditions may also lead to albuminuria. As a rule, however, albuminuria is rare in uncomplicated cases of anæmia, and its appearance is frequently only intermittent in those cases in which it does occur. Albuminuria has been frequently observed in polycythæmia associated with splenic enlargement.

Nucleo-albuminuria has also been demonstrated in some cases of chlorosis [von Noorden (76)], in pernicious anæmia [R. Schmidt (31)], in myelogenous leuchæmia [F. Müller (151), von Noorden (16), Taylor (39)], as well as in lymphatic leuchæmia [Taylor (39), von Stejskal and Erben (87)].

Nucleohistone, which forms, according to Lilienfeld, about 69 per cent. of the dry substance of the leucocytes, has been found by A. Jolles (123) in a case of pseudo-leuchæmia. Kolisch and Burian (152) observed that histone was excreted in the urine of a case of lymphatic leuchæmia. On the other hand, Taylor (39) has sought in vain for histone in two cases of leuchæmia and in one case of pernicious anæmia.

Laache (55) and von Noorden (16) have noted the occurrence of albumoses in pernicious anæmia. Kolisch and von Stejskal (67) found a trace of peptone in their case of "phthisis of the blood." Schmidt (31) also states that he found traces of peptone in two cases of pernicious anæmia. Koettnitz (153) and von Noorden (16) found albumoses in the urine of cases of myelogenous leuchæmia, yet numerous other investigators [*e.g.*, B. Pacanowski (154), von Jaksch (155)] failed to detect albumoses in the urine of leuchæmic patients, and I myself have also frequently sought for them in vain. On the other hand, considerable quantities of a substance, the so-called proteid of Bence-Jones, which possesses a great similarity to the albumoses, but which is regarded by Magnus-Levy (150) as closely allied to the native proteids, have been repeatedly, although not constantly, observed in cases of multiple myelomata. Some of these cases [*e.g.*, Ellinger (157), Senator (158), and Rosen's cases (159)] have at the same time shown the characteristic features of severe anæmia. A combination of an albumin and globulin was present in a case which E. Voit and Salvendi (159A) regarded as belonging to this group. Askanazy (160) also found the Bence-Jones substance in a case of genuine lymphatic leuchæmia. Since, however, he failed to detect it in another case of lymphatic leuchæmia, and since the occurrence of this substance, so far as I know, has not since been demonstrated in any similar case—I myself have been unable to find it in two cases of lymphatic leuchæmia—it may, therefore, be assumed that special conditions were present in Askanazy's case.

7. Sugar, Acetone, Fatty Acids, etc.

The occurrence of sugar is so extremely rare in cases of anæmia and leuchæmia that one is led to think of complications in those cases in which sugar is present in the urine. Goldschmidt (161) gives an account of a

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case of pseudo-leuchæmia with concurrent glycosuria, and Rebitzer (162) reports on a case of diabetes to which leuchæmia became superadded. Von Noorden (76) and Chatin (145) have vainly sought for alimentary glycosuria in chlorosis; Schmidt (31) and Strauss (32) have carried out similar investigations in other severe types of anæmia, especially in pernicious anæmia, with negative results. In view of the observations made by C. Bernard (163), Schenk (164), and others, according to which an increase in the quantity of sugar present in the blood may be experimentally produced by blood-letting, Strauss has investigated the excretion of sugar before and after the withdrawal of blood from two cases of diabetes, and found 3·4 grammes of sugar in the one case in the three days prior to the withdrawal of blood, and 8·8 grammes in the three days succeeding the blood-letting. The corresponding figures in the other case were 31·9 gramme and 36·8 gramme of sugar. The diet of these diabetic patients was naturally the same both before and after the withdrawal of blood.

The excretion of glycuronic acid in severe cases of anæmia is discussed elsewhere. (See index).

Acetone and aceto-acetic acid have been occasionally observed in cases of severe anæmia and leuchæmia [see von Noorden (16)], yet their occurrence has no special relation to the diseases of the blood *per se*, but is dependent upon other factors, especially conditions associated with inanition. Small quantities of acetone may also arise from abnormal formation of fatty acids in the intestines if the oxidizing power of the organism be simultaneously defective (enterogenic acetonuria).

Strauss has conducted quantitative estimations of the fatty acids in one case of pernicious anæmia, and found a value of 70 for the acidity (average of three days), consequently a fairly normal result. Bondzynski and Gottlieb (117) found 0·1367 and 0·1343 gramme as the result of two estimations in a case of myelogenous leuchæmia.

Salkowski (165) found formic and acetic acids in leuchæmia, yet not in larger amounts than they occur in diseases accompanied by increased decomposition of protein. Von Noorden (16) has observed the occurrence of lactic acid in a severe case of pernicious anæmia shortly prior to death. On the other hand, he failed to find it in another case of pernicious anæmia and in two cases of severe posthæmorrhagic anæmia. Körner (166) and Jacubasch (112) state that they found lactic acid in leuchæmia, yet the methods employed for its identification were very inadequate. Salkowski (166) sought for it in vain.

Strauss estimated the oxy-aromatic and hippuric acids in one case of pernicious anæmia, and found the relatively high figure of 40·5. Brieger (175) has also observed the occurrence of high values for their excretion in severe forms of anæmia.

Salkowski (166) found the quantity of oxalic acid (Schultzen's method) rather diminished than increased in a case of myelogenous leuchæmia, and Mohr and Salomon (118) demonstrated the presence of 7·1 and 8·2 milligrammes of oxalic acid per day in a case of myelogenous leuchæmia.

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IV.—THE INFLUENCE OF DISEASES OF THE BLOOD ON DIGESTIVE PROCESSES.

1. The Secretion of Hydrochloric Acid.

Since Manassein (204) has given experimental proof that the production of hydrochloric acid by the stomach decreases, and may even completely cease after the withdrawal of considerable quantities of blood, numerous clinical investigations of the secretion of gastric juice in the various forms of anæmia—above all, in chlorosis and pernicious anæmia—have been carried out. Further, this problem has been again investigated by London and Sokoloff (204A), with the aid of the experimental procedure devised by Pawlow. These authors found a *secretio tarda abundans hypopeptica* as the result of the withdrawal of 37 per cent. of the total blood from the circulation of a dog. Two or three weeks after the withdrawal of blood there appeared a *hypersecretio initialis*, which formed a transition stage to normal conditions. F. Riegel (205) and his pupils (206, 207) obtained results which indicated that a hyperacidity is to be found relatively frequently in cases of chlorosis, and that the occurrence of a subacidity is exceptional. On the other hand, A. Ritter and others (208, 209, 210) found that subacidity was the more frequent condition. At a later date the observations which emanated from Riegel's clinique were confirmed by von Noorden (76) (twenty-five cases), as well as by Schätzel (211) (thirty cases), in von Leube's clinique. Hayem (212) found hyperacidity in forty-two cases out of a total of seventy-two. I have found hyperacidity in somewhat more than half my cases. Further, Cantu has also frequently found hyperacidity in the more protracted forms of chlorosis; while T. Rosenheim (213), Buzdygan and Glucinski (214), Maurer (215), Schroth (216), Lenhartz (217), H. Schneider (218), and others, have not been able to establish the existence of any such marked preponderance of hyperacidity. The characters of the gastric secretion are usually very variable in cases of secondary anæmia, yet in these conditions the tendency to subacidity is generally more frequent than that to hyperacidity.

O. Schaumann (219) found free hydrochloric acid in one out of a total of eleven cases of pernicious anæmia. Rosenqvist (62) observed apepsia gastrica in eleven out of twenty cases, absence of free hydrochloric acid with a total acidity of 22 and 28 in the absence of lactic acid in two of these cases, and normal or increased acidity associated with the presence of free hydrochloric acid in the remaining seven cases. A total acidity of 84 was demonstrated in one out of three cases examined by Rosenqvist in which hyperacidity was present, and an acidity of 100 in another of these cases. A statistical review by Faber and Bloch (220) showed that more or less distinct subacidity or absence of acid was present in by far the larger number of cases of pernicious anæmia, for free hydrochloric acid was present in only one out of the total thirty-three observations collected by these authors. Schaumann's cases were also comprised in this total. Free hydrochloric acid was not demonstrable in von Moraczewski's four cases (40). I found free hydrochloric acid in

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only two out of eight cases. Bloch (61), however, states that a rise in the excretion of hydrochloric acid in pernicious anæmia is possible as a result of temporary improvement.

Pepsin was found to be absent in a case of pernicious anæmia examined by von Moraczewski (40), and I have also twice vainly sought for pepsin by means of Mett's method.

It is exceptional to find the motility of the stomach reduced in cases of chlorosis, or in cases of secondary and of pernicious anæmia. There is sometimes even an abnormally rapid disappearance of the ingesta from the stomach in those cases of pernicious anæmia in which an apepsia gastrica is present, as well as in other cases of apepsia gastrica.

Little is known with regard to the condition of the gastric functions in leuchæmia or pseudo-leuchæmia. I myself found normal conditions in one case of myelogenous, as well as in one of lymphatic, leuchæmia. I found normal motility with slight subacidity (no free hydrochloric acid, total acidity 29) in a case of anæmia splenica. Reinhold (220A) failed to find free HCl in the gastric contents of a case of polycythæmia without enlargement of the spleen, resulting from chronic poisoning with carbon monoxide, while Weintraud (124D) met with hyperacidity in a similar case accompanied by enlargement of the spleen. Such isolated observations, however, may be more or less dependent upon chance, and must be first controlled by serial investigations.

2. The Chemical Characters of the Bile.

Under the direction of F. Müller, Kumara (237) has carried out investigations on the post-mortem characters of the bile in various forms of anæmia. He found in one case of pernicious anæmia a relatively high colour coefficient, a fairly normal dry residue, a relatively high specific gravity, only a slight decrease in viscosity, a normal amount of urobilinogen, and a fairly large amount of urobilin. The colour, the viscosity, as well as the quantities of urobilinogen and urobilin, were considerably diminished in three cases of severe acute posthæmorrhagic anæmia, and a normal amount of urobilin was found in only one case of gastric hæmorrhage. The dry residue was normal in amount, except in the case of gastric hæmorrhage. The specific gravity was not lowered. The latter was not determined in the case of gastric hæmorrhage.

Von Noorden has carried out quantitative estimations of the urobilin in the fæces. He found 0·021 and 0·029 gramme in two cases of chlorosis, and 0·920 gramme in one case of pernicious anæmia. If what is known with regard to the quantity of urobilin present in the urine in anæmia is taken into consideration, the above-mentioned investigations possess a certain interest in connection with the pathogenesis of pernicious anæmia.

3. The Absorption of Food.

F. Müller and Wallerstein (68) (duration of investigation six days), and Lipmann-Wulff (71) (three cases investigated for five to seven days) found a normal utilization of nitrogen and fat in severe chlorosis. The nitrogen

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of the food was also well utilized in Henius's case (15) (duration of investigation eight days). The loss of nitrogen in the fæces amounted in Vannini's five cases (75) to 10·02 and 10·84 per cent. only in two instances, and the loss of fat amounted to 9·25 per cent. in only a single instance. The amounts lost were less in the remaining cases. The percentage amount of carbohydrate present in the fæces only exceeded 0·5 per cent. in a single case. The so-called grey-coloured fæces of chlorotic patients [von Jaksch (221), Nothnagel (222)] represent a rare and usually transient phenomenon, the cause of which is still not fully explained. Von Noorden (76) was unable to find any excessively large amount of fat in the fæces of a case belonging to this type. I was also able to demonstrate the occurrence of such fæces in a case in which grey-white fæces were passed for a whole week after the administration of a test diet. The fæces in this case gave a red coloration with the corrosive sublimate test (urobilin). No signs of icterus were present in the foregoing case.

P. Jacob and Bergell (90) found a high loss of nitrogen amounting to 16·6 per cent. in a severe case of secondary anæmia as the result of an investigation lasting twelve days.

Von Noorden (223) found a loss of nitrogen in the fæces of patients suffering from pernicious anæmia amounting to 5·6 per cent. (average of seven days) and 4 per cent. (average of fifteen days), and a loss of fat amounting to 11·4 and 3·66 per cent. respectively. Schmidt (31) found in his Case I., as the result of six days' investigation, an average loss of nitrogen of 11·66 per cent., and in his Case II. an average loss of nitrogen amounting to 12·3 per cent. (average of three days). Von Moraczewski (40) found a loss of nitrogen of 15·2 per cent. in Case II., and one of 12·9 and 15 per cent. in Case IV. The loss of nitrogen amounted to 17 per cent., that of the fat to 13·5 per cent. (average of four days), and that of carbohydrate to 1·6 per cent. in von Stejskal and Erben's case (59). Strauss (60) found a loss of nitrogen of 8·2 per cent. (average of ten days), and a loss of fat of 8·7 per cent. in one case. The corresponding figures in a second case were 9 per cent. and 7·8 per cent. (average of two days). On the other hand, Bernert and von Stejskal (64) found a loss of nitrogen amounting to 19·7 and 21·2 per cent. respectively (averages of three days) in two cases. The supply of nitrogen in the food was rather meagre in the latter cases. Rosenqvist (62) found a nitrogen loss of 8·05 per cent. (average of six days) in a case belonging to the cryptogenetic form of pernicious anæmia. The loss of nitrogen amounted to 5·1 per cent. in his second case (duration of investigation twenty-four hours), to an average of 5·7 per cent. (average of nineteen days), to 9·2 per cent. (average of eight days), and to 6·4 per cent. (average of fifteen days) in the same case during different periods of the disease. The loss of nitrogen in the fæces amounted to 7·3 per cent. (average of twelve days), 10·1 per cent. (average of eleven days), and to 8·8 per cent. (average of twelve days) in Rosenqvist's Case III. Bloch (61) found a loss of nitrogen of 12 per cent. in one case (average of ten days) and 9·73 per cent. in a second case (ten days). Loewy (95) found losses of nitrogen and of fat in the fæces amounting to 10·5 and 3·3 per cent. respectively in a case of anæmia splenica.

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Bohland (63) reports a loss of 11 to 13 per cent. of nitrogen in two cases of anæmia due to anchylostoma, while the utilization of fat was normal. Battistini and Micheli (224) likewise found a considerable loss of nitrogen (12·18 per cent.), and only a slight loss of fat. Vannini (65A) determined a diminished utilization of nitrogen in four out of five cases of anæmia due to anchylostoma (the nitrogen of the fæces varied from 10·36 to 19·71 per cent.), as well as a diminished utilization of fat in two cases (quantities of fat in the fæces 10·47 and 14·0 per cent.). Schupfer and de Rossi (41) likewise found that the fat was well absorbed in their three cases, and that the absorption of nitrogen was slightly diminished.

The following data dealing with the nitrogen lost in the fæces in cases of anæmia due to bothriocephalus have been calculated from Rosenqvist's tables :

Case.		Per Cent.
I. (five days)	=	11·7
IV. (seven days)	=	16·6
VI. (four days)	=	12·3
VII. (six days)	=	15·3
VIII. (thirteen days)	=	6·0
IX. (five days)	=	18·7
X. (five days)	=	14·2
XI. (ten days)	=	15·5
XII. (sixteen days)	=	7·5
XIII. (seven days)	=	10·4
XIV. (seven days)	=	8·0
XV. (forty-three days)	=	10·3
XVI. (seven days)	=	7·8
XVII. (fourteen days)	=	18·3

A review embracing the results obtained by different observers in cases of pernicious anæmia demonstrates that the quantity of nitrogen excreted in the fæces sometimes exceeds the average, or even the upper normal limit. This statement holds good to a marked extent, or, at least, not infrequently in those forms of anæmia due to helminthes. An increase in the excretion of nitrogen exceeding the normal limits is, however, by no means a constant feature. On the contrary, in a whole series of cases—more frequently in the cryptogenetic types of pernicious anæmia than in those due to helminthiasis—values are present which lie distinctly within the normal limits. If the total quantity of nitrogen actually absorbed in individual experiments be considered, it appears that the quantity of nitrogen absorbed was in the great majority of cases so large as to completely suffice for the nutrition of the patient examined. One can, therefore, scarcely agree with certain authors—*e.g.*, Eisenlohr (225), Martius (226), and others—in regarding a diminution in the absorption of nutriment as a possible cause of pernicious anæmia, for even the results obtained with regard to the utilization of fat are by no means favourable to this view. The utilization of fat was good on the average, with the exception of von Stejskal and Erben's case (59), in which the quantity of fat supplied per day only amounted to 60·2 grammes. As a matter of fact, the problem of fat absorption can be much more readily decided than that of the utilization of nitrogen,

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for it does not appear to be excluded that part of the fæcal nitrogen was secreted by the intestinal wall in those cases in which relatively high values were obtained for the nitrogen of the fæces. In this connection it is known from pathological investigations that infiltrations of the mucous membrane with leucocytes mainly belonging to the mononuclear type are not at all infrequent occurrences in cases of pernicious anæmia. These infiltrations imply the presence of pathological processes in the intestinal wall, with consequent loss of protein. At all events, "the atrophy of the intestinal wall," which was formerly so frequently discussed in this connection, and which I myself (197) was only able to demonstrate in six out of ten cases, no longer possesses the same interest as it did formerly, since Faber and Bloch (220 and 227), in continuing Heubner (228) and Gerlach's work (229), have proved that these features, when occurring in pernicious anæmia, are not the consequence of atrophy, but of an abnormal distension of the alimentary canal, due to a post-mortem development of gas within it. Even Nothnagel (230) has finally expressed himself as sceptical with regard to the existence of intestinal atrophy.

Pettenkofer and Voit (6), as the result of one day's observation, and Fleischer and Penzoldt (81), as the result of observations extending over five days, have observed losses of nitrogen in the fæces amounting to 17 to 17·7 per cent. The loss of fat amounted to 7 per cent. in Pettenkofer and Voit's case. As the result of investigations extending over three days, May (46) found a loss of nitrogen amounting to 5·6 per cent., and a loss of fat of 6 per cent., in a patient suffering from myelogenous leuchæmia and maintained on a purely milk diet. Von Moraczewski (84) records a nitrogen loss of 4·4 per cent. in a case of myelogenous leuchæmia, which was investigated for six days. The loss of nitrogen amounted to 8·95 per cent., and that of fat to 2·5 per cent., in von Stejskal and Erben's (87) case of myelogenous leuchæmia (period of investigation five days). Von de Wey found in his first series of experiments (ten days) on the utilization of nitrogen in his Case I. a loss of nitrogen of 9·06 per cent. and a loss of fat of 5·3 per cent., a loss of nitrogen amounting to 5·63 per cent. and of 6·2 per cent. in his second series (ten days); in his third series a loss of nitrogen of 5·27 per cent., and one of fat of 8·7 per cent. (average of eight days); and in his fourth series a loss of nitrogen of 9·1 per cent., and one of fat of 10·4 per cent. (five days). The loss of nitrogen amounted to 9·7 per cent., that of fat to 5·5 per cent., in de Wey's Case II. Von Stejskal and Erben found in a case of chronic lymphatic leuchæmia a loss of nitrogen in the fæces amounting to 18·6 per cent., and one of fat amounting to 22·2 per cent. On the other hand, Botazzi and Orefici (85) found that the absorption of fat was normal in a case of lymphatic leuchæmia. In a case of acute leuchæmia Magnus-Levy (14) observed a loss of nitrogen amounting to more than 12 per cent. (seventeen days' experiment). The daily supply of fat was in this case 39 grammes. Moraczewski (84) found a nitrogen loss of 12·6 per cent. in a case of pseudo-leuchæmia (period of investigation seven days).

These figures are somewhat similar to those obtained in pernicious anæmia, and permit the inference that numerous cases of the foregoing

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types, especially those of myelogenous leuchæmia, show a perfectly normal absorption. Even in those cases in which large quantities of nitrogen were present in the fæces the high values for the fæcal nitrogen need not invariably, and under all circumstances, be due to nitrogenous material which had escaped absorption, since Weintraud (231) has demonstrated the fact that the fæces in leuchæmia contain about ten times the normal average amount of xanthin bodies. The normal quantity varies from 0·02 to 0·1 gramme purin nitrogen. (See references 232, 233 for fuller details.)

Since the xanthin bases of the fæces do not originate from the nuclein of the food, but may be regarded as derivatives of nucleins produced by the intestinal wall or the glands connected with it, and of the intestinal bacteria, they consequently possess a special interest in virtue of this origin.

The sodium chloride and iron are the chief constituents of the ash which should be mentioned. Normally, fæces contain the merest traces of sodium chloride. Von Hösslin (234) has maintained that the quantity of iron in the fæces is increased.

Von Moraczewski (40) found a daily chloride excretion of 0·231 gramme in Case I. of pernicious anæmia, one of 0·021 gramme in Case II., one of 0·97 gramme in Case III., and one of 0·018 gramme in Case IV. Von Stejskal and Erben (59) found 0·466 gramme NaCl in one case (four days' experiment), and Strauss observed 0·17 gramme NaCl per day in the fæces of his Case I. (ten days' experiment) (60).

Von Hösslin (234) found that the quantity of iron present in the fæces of chlorotic patients was greater than that found in the case of healthy individuals. The figures given by von Hösslin represent percentages calculated for dried fæces, and consequently do not permit a calculation of the total amount excreted daily. Von Hösslin regarded these results as supporting the view that latent intestinal hæmorrhages are to be held responsible for the production of chlorosis. Lloyd Jones (235) also supports this theory. O. Rossel (236), however, has recently been unable to convince himself of the frequent occurrence of blood in the fæces. The latter observer employed the aloin test for blood, which, according to my experience, is an excellent test for the presence of blood.

Certain investigations upon the intestinal decomposition of fats are of interest in connection with the condition of the digestive secretions in chlorosis. Thus, von Noorden found 77 and 81 per cent. of the total fat in the form of fatty acids and soaps in two cases of severe chlorosis. Strauss reports 52 per cent. of the total fat decomposed into fatty acids and soaps (40 per cent. as fatty acids, 12 per cent. as soaps) in Case I. of pernicious anæmia, while in Case II. the corresponding figures were 72 per cent. (52 per cent. as fatty acids, 20 per cent. as soaps).

Müller (234A) has recently observed peculiar crystals, which assume an intensely brown-red colour on treatment with Lugol's solution, in the fæces of cases of pernicious anæmia.

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4. Processes of Decomposition in the Intestinal Canal.

Since mention has already been made of various results which were obtained in regard to the presence in the urine of decomposition products of intestinal origin (pp. 385-387), it need only be noted here that certain observers have surmised the existence in pernicious anæmia and leuchæmia of etiological connections between abnormal processes of decomposition in the alimentary canal and the development of the disease. Duclos (191), Sir Andrew Clark (192), Bouchard (193), Couturier (194), Nothnagel (195), Hunter (202B), and others, have given expression to the view that the constipation so frequently present in chlorosis exercises an injurious influence on the blood, owing to the formation of abnormally large quantities of toxic decomposition products. Various observers [Hunter, Vannini, Ewald, E. Grawitz, Wiltschur (60), and others] have not only held certain toxic substances secreted by intestinal parasites—*e.g.*, *Bothriocephalus latus* and *Anchylostoma duodenale*—to be responsible for the development of pernicious anæmia, but have also sought to explain cases of the cryptogenetic type by the hypothesis of an intestinal intoxication. Köttnitz (153) regards leuchæmia as due to poisoning with peptone, and Vehsemeyer (196) has also considered the possibility of active factors of intestinal origin as the causes of leuchæmia, since opportunities of observing pathological phenomena of intestinal origin occur not only in the initial stages of leuchæmia, but also during the later course of the disease. No satisfactory proof for the foregoing theories has so far been obtained, for no increased excretion of indican, ethereal sulphates, volatile fatty acids, ptomaines, or other constituents of the urine which indicate increased intestinal putrefaction, has been demonstrated in the majority of cases of chlorosis, of pernicious anæmia, or of leuchæmia. Further, I have repeated Vannini's (197) experiments with certain technical improvements. These investigations aimed at the production of alterations in the blood of rabbits, as the result of an artificial intestinal obstruction. I was only able to determine a slight reduction in the number of erythrocytes without any distinct alterations in the size or form of the red blood-corpuscles, or any perceptible alteration in the amount of hæmoglobin. Further, the hæmolytic action of the blood-serum of the rabbits experimented on was in no way different from that of animals with unobstructed rectum. These observations are, therefore, opposed to those of Vannini (197), as well as to those of Kasnow (199), who had found more or less intense alterations in the red blood-corpuscles after ligature of the rectum. Bloch's experiments (61) yielded results supporting my conclusions. He injected extracts of the fæces of healthy individuals and of patients suffering from Biermer's anæmia into the circulation of animals. The fæcal extracts from the cases of Biermer's anæmia likewise showed no greater toxicity than similar extracts of normal fæces. Since I also was unable to demonstrate any increase above the normal in the hæmolytic activity of blood-serum obtained from patients suffering from severe forms of chronic constipation, I therefore still maintain the opinion which I have already expressed—that the material at present available

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is insufficient adequately to support the theory that the foregoing diseases arise as a consequence of enterogenic auto-intoxication. At the same time, it cannot be denied that intestinal disturbances are more or less frequent in cases of anæmia. These disturbances appear more frequently in the form of constipation in cases of chlorosis, and more frequently in the form of diarrhœa in cases of pernicious anæmia. Such disturbances, which, as has already been indicated, certainly lead to anomalies in the gastric and intestinal secretions, may, however, be regarded rather as the consequence than as the cause of the anæmia. As a matter of fact, apepsia gastrica, such as occurs in pernicious anæmia, produces to a certain extent a predisposition to diarrhœa, and an increased growth of the lymphatic tissue present in the intestinal wall has been not infrequently observed in pernicious anæmia as well as in cases of leuchæmia [see Litten (200), Koch (201), Schaumann (202), Strauss (60 and 198), Bloch and H. Hirschfeld (202A), and others]. Possibly a farther development of the available methods may provide the means of obtaining more accurate proofs of the existence of enterogenic auto-intoxications. Yet even when these conditions appear to be fulfilled, it must still be borne in mind that, when the quantity of excretory products of intestinal origin present in the urine is increased, this increase, as has already been mentioned, may be due to a reduction in the transformations undergone by the intestinal toxines within the tissues of the organism, this reduction being a result of the anæmia. Such a theory is in no way weakened by the fact that a favourable influence on the course of the anæmia has been observed as the result of an improvement of nutrition and the application of other means for the treatment of gastro-intestinal disturbances.

V.—THE INFLUENCE OF DISEASES OF THE BLOOD ON THE CHEMISTRY OF THE BLOOD AND TISSUES.

A.—CHEMISTRY OF THE BLOOD AS A WHOLE AND OF THE BLOOD-SERUM.

1. Osmotic Concentration.

The osmotic concentration of the blood is, according to von Koranyi (63), frequently abnormally low, yet normal values are also not infrequently found. At least, Kossler (238) observed that the values varied from $-0{\cdot}55°$ to $-0{\cdot}56°$ in chlorosis, and from $-0{\cdot}54°$ to $0{\cdot}565°$ in secondary anæmia. Strauss found depressions of the freezing-point of $-0{\cdot}56°$ and $-0{\cdot}57°$ in pernicious anæmia, and $-0{\cdot}56°$ in a case of very severe secondary anæmia; $-0{\cdot}52°$ in another case of similar character. Landau (239) gives values of $-0{\cdot}53°$ and $-0{\cdot}56°$ in two cases of pernicious anæmia. I found $-0{\cdot}55°$ in Banti's disease, $-0{\cdot}59°$ in myelogenous leuchæmia, and Rumpfel (243A) noted a like depression in leuchæmia. Investigations carried out on men by von Limbeck (240), Köppe (241), H. Hamburger (242), M. Löper (243), and myself, show that, if any alterations do occur in osmotic pressure, they are only slight in degree.

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Ceconi and Micheli (244), as well as Bickel and Fraenckel (245), found the electrical conductivity of the blood-serum normal in amount in cases of chlorosis.

2. Specific Gravity.

Numerous investigations are available with regard to the specific gravity of the blood (41, 238-253). The most general result of these is that a diminution in the specific gravity of the blood may occur in almost all diseases of the blood. According to Grawitz (141), the specific gravity of the blood varies from 1035 to 1045 in cases of chlorosis, yet lower results have also been observed when complications were present. The latter, however, can no longer be regarded as pure cases of chlorosis simplex. Thus, Askanazy (256), amongst others, found a reduction in the specific gravity of the blood in severe forms of chlorosis and of secondary anæmia. One finds not infrequently values lying below 1035 in severe forms of secondary anæmia, especially in cases of carcinomatous cachexia and after severe hæmorrhages. Thus, I myself noted a value of 1028 in a severe case of anæmia due to carcinoma, and Grawitz (141) observed a specific gravity of 1025 in one case of gastric hæmorrhage. Values under 1030 have been found by different authors, especially in cases of pernicious anæmia. Baginsky found on one occasion a specific gravity of 1020 in the case of a child suffering from pernicious anæmia, and I myself had an opportunity of observing a value of 1021 in a case of pernicious anæmia. Weintraud (124D) found values varying from 1057 to 1067 in polycythæmia associated with enlargement of the spleen, and Preiss (256A) noted a value of 1065 in the same disease. A reduction in the specific gravity of the blood was also demonstrated by Schupfer and de Rossi (41) in anæmia due to anchylostoma. Dieballa (254) found values varying from 1042 to 1060 in the case of leuchæmia. Askanazy (256) found values varying from 1038 to 1060·5 in the same disease. According to Grawitz, values as low as 1036 may occur even in leuchæmia.

The specific gravity of the blood-serum is generally lowered to a considerably less extent than that of the blood as a whole in cases of chlorosis, secondary anæmia, and pernicious anæmia. One meets with a reduction in the specific gravity of the blood-serum more frequently in cases of chronic losses of blood and in anæmia resulting from malignant tumours than in cases of pernicious anæmia. In fact, the contrast between the marked reduction in the specific gravity of the blood as a whole and the relatively slight alteration in the specific gravity of the blood-serum is often a striking feature of the latter disease. A reduction in the specific gravity of the blood-serum sometimes also occurs in cases of chlorosis "gravis," as distinguished from chlorosis "simplex." The specific gravity of the blood-serum lies, as a rule, within more or less normal limits in the latter condition. Becquerel and Rodier (257) found an average specific gravity of 1028·1 in chlorosis simplex, and Hammerschlag (258), as well as Askanazy, found the specific gravity at least not lower than 1027 in this disease. Weintraud's (124D) values in poly-

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cythæmia associated with splenic enlargement varied between 1025·3 and 1026·6.

Geisbock (257A) found a specific gravity of 1066 to 1067 in polycythæmia which was not accompanied by splenic enlargement. Askanazy's values lay between 1020 and 1035 in leuchæmia of the mixed cellular type. I found on two occasions the specific gravity to be 1025 in leuchæmia, and Magnus-Levy (14) observed a specific gravity of 1025·5 in one case of the same disease.

3. Dry Residue.

The dry residue of the blood as a whole was found by Stintzing and Gumprecht (259) to be reduced in all forms of anæmia. These authors found the amount of the dry residue of the blood sometimes reduced to half the normal in carcinoma ventriculi, yet such low results are by no means to be regarded as forming the rule. Krüger (260), Stintzing and Gumprecht (259), S. von Moraczewski (261), as well as Jellinck and F. Schiffer (262), also noted values as low as 10 per cent. or even lower in such cases. The lowest value obtained by Jellinck and Schiffer (262) amounted to only 9·15 per cent., that of S. von Moraczewski to only 8·61 per cent. Kossler (238) and Moritz (263) also obtained very low results.

Grawitz (141) observed values as low as, or even lower than 10 per cent. in some cases of pernicious anæmia. Rumpf-Dennstedt (264) gives in one instance a value as low as 9·95 per cent., and Moritz (263) also obtained a value of 9·6 per cent. in one instance. Von Moraczewski (261) noted on one occasion a value of 8·59 per cent., and Erben obtained a value of only 8·43 per cent. in one case. The dry residue amounted to not more than 12 per cent. in two cases investigated by Stintzing and Gumprecht (259), as well as in one case of Biernacki (255) and one of Sawjalow's.

Different observers [Biernacki, Stintzing and Gumprecht, Kössler, Grawitz, von Noorden (76), von Moraczewski, Askanazy, Jellinck and Schiffer, Maxon, O. Moritz] have observed values in chlorosis which sometimes were normal, sometimes lay at the lower limit of the normal, and at other times must be regarded as abnormally low. Values of less than 12 per cent. have been observed by Biernacki, Stintzing and Gumprecht, von Noorden and Maxon (267). As a rule, however, it may be taken that the amount of the dry residue of the blood as a whole more frequently approximates to the normal in cases of chlorosis than in other forms of anæmia.

Weintraud (124D) found values lying between 22·68 and 29·03 per cent. in polycythæmia associated with enlargement of the spleen. Geisböck (257A) noted values lying between 24·83 and 26·48 per cent. in polycythæmia, which was not accompanied by splenic enlargement.

A more or less marked reduction in the amount of the dry residue of the blood was also found in leuchæmia and pseudo-leuchæmia. Thus, Mosler found values lying between 18·4 and 11·9 per cent. in leuchæmia; Krüger (260) a value of 18·63 per cent.; Freund and Obermayer (268)

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a value of 10·4 per cent.; Askanazy (256) values varying from 13·76 to 19·52 per cent. in leuchæmia of the mixed cellular type; Biernacki a value of 18·95 per cent.; Erben (269) values of 13·8 and 15·0 per cent. respectively in a case of lymphatic leuchæmia; and Moritz a value of 18·7 per cent. in one case. Stintzing and Gumprecht found 15 per cent., and von Moraczewski, as well as Moritz, 17 per cent. of dry residue.

Kossler (238), Erben (270), and Askanazy (256) found over 8 per cent. of dry residue in the blood-serum of cases of chlorosis. Grawitz (141), however, observed values of 7·28 and 7·6 per cent. in two severe cases. Biernacki (255) and von Limbeck (240) found along with normal values percentages as low as 7·73, 7·20, and 6·48 in cases of chlorosis. It may be doubted, however, whether the latter were cases of chlorosis "simplex" or of chlorosis "gravis." Kossler (238) found a value of 8·05 per cent. in one case of secondary anæmia, and Biernacki (255) one of 7·1 per cent. in another case of the same disease. Popp (269A) found 7·84 per cent. of dry residue in one case of anæmia due to carcinoma. Strauer (269B) found 10·9 per cent. in one instance, and subnormal values of 8·5 to 6·8 per cent. in five instances out of a total of ten similar cases. Coenen (269C) found 6·0 per cent. in a case of gastric carcinoma. Askanazy (256) determined values of 7·2 to 9·1 per cent., and of 6·2 per cent. in a case of carcinoma ventriculi complicated with hæmatemesis. Erben (269D) noted a percentage of 8·3 in one case of gastric carcinoma. Erben found 6·6 per cent. of dry residue in one case of pernicious anæmia, Askanazy (256) values of 6·24 and 7·21 per cent., and Sawjalow (266), as well as Landau (239), a value of 7·41 per cent. in other cases of the same disease. Krüger (360) also found 6·15 per cent. of dry residue in one case of severe anæmia. Weintraud (124D) found, as the result of two estimations, a value of 9·3 per cent. in his case of polycythæmia, and Reckzeh (270A) one of 7·06 to 7·8 per cent. in another case of similar nature. Erben (268) noted values of 8·8 and 9·8 per cent. in lymphatic leuchæmia, and Krüger (269) found 11·9 per cent. of dry residue in myelogenous leuchæmia. Freund and Obermayer (267) found 10·4 per cent. in another case of myelogenous leuchæmia. Askanazy's values varied from 6·25 to 11·77 per cent. of dry residue, and Strauss (298A) found a value of 9 per cent. in a case of leuchæmia of the mixed cellular type. Magnus-Levy obtained 8·2 per cent. of dry residue in acute leuchæmia.

4. Amount of Protein present in the Blood.

Kossler (238) found that the quantity of protein present in the blood as a whole, which normally corresponds to 3 per cent. of nitrogen in the form of protein, was diminished to about two-thirds of the normal in two cases of severe chlorosis. Von Moraczewski found that the quantities excreted were usually normal, or only slightly reduced, in chlorosis; yet one case of chlorosis gravis, in which the number of erythrocytes was only slightly more than half the normal, yielded values of only 1·66 per cent. nitrogen. Erben (270) also noted values varying from 1·73 to 2·25 per cent. nitrogen in three cases of chlorosis. Kossler (238) found values

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of 2, 2·4, and 2·7 per cent. nitrogen in secondary anæmia, and v .Moraczewski (261) obtained values which were usually, but not invariably, reduced below the normal, and which in one case lay as low as 1·22 per cent. Erben (265) found a value of 1·08 per cent. nitrogen in pernicious anæmia, Moraczewski (261) one of 1·24 per cent. nitrogen, Sawjalow (266) one of 1·38 per cent. nitrogen, and Brandenburg (271) a value of 1·9 per cent. nitrogen in other cases of the same disease. Grawitz (14) noted values as low as 1·03 per cent. nitrogen, consequently numerical results which are not higher than those which one meets with in the blood-serum. Weintraud (124D) found two values of 3·4 per cent. nitrogen in polycythæmia with enlargement of the spleen, and Reckzeh (270A) 4 and 4·1 per cent. nitrogen in another case of the same disease. Erben (269) observed values of 1·81 and 2·05 per cent. nitrogen in lymphatic leuchæmia, and Freund and Obermayer determined a value of 1·15 per cent. nitrogen in a case of leuchæmia of the mixed cellular type. The value amounted to 1·73 per cent. nitrogen in a case of acute leuchæmia examined by Magnus-Levy (14). Brandenburg (271) found 2·24 per cent. and von Moraczewski (261) 2·70 per cent. nitrogen in pseudo-leuchæmia.

Von Limbeck (240) found in one instance 1·08 per cent. nitrogen in the form of protein in the blood-serum of a case of chlorosis, and 0·79 per cent. nitrogen in another case. Kossler (238) noted values of more than 1·2 per cent. nitrogen in two instances, and 1·15 and 1·16 per cent. nitrogen in a third instance. The percentages of nitrogen varied from 1·11 to 1·28 in three cases of chlorosis examined by Erben (270). Dieballa (254) obtained approximately normal results in five cases of chlorosis. Kossler (238) found 1·23 per cent. nitrogen in one case of secondary anæmia, and 1·11 and 1·125 per cent. nitrogen in two other cases. Erben (265) found a nitrogen content of 0·84 per cent. in pernicious anæmia; Sawjalow (266) a value of 0·95 per cent. nitrogen in another similar case; Ruttan and Adami (272) 0·83 per cent. nitrogen; and Strauss (60) a value of 1·12 per cent. nitrogen in other cases of the same nature. Landau (239) found 1·09 and 1·07 per cent. nitrogen in pernicious anæmia, and Dieballa 1·52 per cent. nitrogen in a case of the same disease. Weintraud (124D) obtained 1·34 and 1·37 per cent. nitrogen in his cases of polycythæmia associated with enlargement of the spleen. Erben (269) found 1·09 and 1·26 per cent. nitrogen in lymphatic leuchæmia, and Strauss 1·01 per cent. nitrogen in the same disease. Magnus-Levy observed a nitrogen value of 1·14 per cent. in myelogenous leuchæmia, and Strauss (273) 1·33 per cent. nitrogen in another case. Taylor (39) states that he found a normal amount of protein in the blood-serum of several cases of leuchæmia. Brandenburg (271) found 0·93 per cent. nitrogen in the form of protein in pseudo-leuchæmia.

More recent investigations, which I have carried out partly alone and partly in conjunction with Chajes (274) by means of the refractometric method of examining the blood-serum, have yielded results in numerous cases of chlorosis, of secondary anæmia, of pernicious anæmia, of leuchæmia, and of pseudo-leuchæmia, which almost invariably corresponded to a nitrogen content of more than 1 per cent. I only found a value slightly below 1 per cent. in one case of very severe posthæmor-

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rhagic anæmia. With the aid of the same method Reiss (275) obtained in leuchæmia a result which would correspond with a protein content of more than 1·2 per cent. In agreement with a previous reference (274), I have carried out in the intervening period a series of investigations dealing with the relation of the value for the specific gravity of the blood as a whole to the refraction value. If, in accordance with the formulæ suggested, the last two places of the refraction value are divided by the last two places of the value for the specific gravity of the blood as a whole, one normally obtains a concentration coefficient of approximately 1·6 to 1·8, and only rarely one as high as 2. As the result of seven estimations, I have on six occasions obtained values in three cases of pernicious anæmia which varied from 2·05 to 3. In one instance a value of 1·79 was obtained. On the other hand, the quotient rarely exceeded the figure 2 in severe forms of anæmia resulting from carcinoma or pulmonary tuberculosis. As a rule, the quotient lay within normal limits, or even below 1·5 in such cases.

5. Relative Proportions of the Protein Substances present in the Blood.

Becquerel and Rodier (257) found 3 per cent. of fibrin in the blood as a whole in cases of chlorosis, whereas normal blood contains only 1·9 to 2·2 per cent. of fibrin. The quantity of hæmoglobin varied from 46·9 to 52·2 per cent. of the total protein present in the blood of three cases of chlorosis reported on by Erben, and the quantity of serum albumin and that of serum globulin amounted to 25·5 and 21 per cent. respectively of the total protein in the single case in which these protein substances were separately estimated. In two of these cases the quantity of fibrin amounted to 2·8 and 3·5 per cent. of the total protein. In anæmia due to carcinoma Erben (269D) noted that 2·1 per cent. of the total protein consisted of albumin, 1·2 per cent. of globulin, and 1·6 per cent. of fibrin. The relative proportions in pernicious anæmia were 55·6 per cent. of albumin, 13·5 per cent. of globulin, and 1·93 per cent. of fibrin (265). Krüger (260) observed that the quantity of fibrin contained in the blood amounted to 0·31 per cent. in a case of severe anæmia. Erben (269) found 32·1 per cent. of the total protein in the form of albumin, and 16 per cent. in the form of globulin in lymphatic leuchæmia. The quantity of fibrin present in the blood of one case of the latter disease amounted to 2·9 per cent. of the total protein, and to 1·88 per cent. of the total protein in the other case.

In cases of chlorosis Limbeck and Pick (276) estimated the quantity of globulin present in the blood-serum in percentages of the total protein. They found 34·53 per cent. of globulin in one instance, and 38·3 per cent. in another. Erben (270) found 45·1 per cent. of globulin in one case of chlorosis. Erben (269D) found 63 per cent. of albumin and 36 per cent. of globulin in anæmia secondary to carcinoma, and Limbeck and Pick noted 43·9 and 72·9 per cent. of albumin, and 27·2 and 56·1 per cent. of globulin, under similar conditions. On the other hand, Erben found only 19·5 per cent. of globulin in pernicious anæmia, as compared with 40·7

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per cent. in the healthy individual [Hammarsten (277)]. Ruttan and Adam (272), however, found 44·2 per cent. of globulin in a case of pernicious anæmia. Erben (269) found 33·3 per cent. of the protein in the form of globulin in lymphatic leuchæmia. Although these results appear to indicate that the quantity of globulin is more frequently reduced than increased in diseases of the blood, yet Erben's surmise that the formation of globulin from the products of intestinal digestion is very markedly hindered in pernicious anæmia, still requires further thorough investigation. Pfeiffer (278) found that the quantity of fibrin present in the blood-plasma was scarcely increased in three cases of leuchæmia. This observation, as well as the similar one made by Erben, deserve special attention, in view of the facts that Hoffmann (279) has found a high percentage of fibrin in posthæmorrhagic leucocytosis, and that Pfeiffer himself has found a similar rise in the quantity of fibrin in inflammatory leucocytosis. The latter result induced Pfeiffer (280) to investigate the quantity of fibrin present in the blood of leuchæmic patients. He found the quantity normal in both forms of leuchæmia.

Nucleo-albumin was found post-mortem by Matthes (86) in the blood of a leuchæmic patient.

6. Products of Protein Decomposition occurring in the Blood.

Amongst the products of protein decomposition, the albumoses amino-acids, xanthin bodies, and uric acid are of primary interest.

The occurrence of albumoses in the blood has been specially studied in cases of leuchæmia, but the investigations have not all been carried out on the blood during life. On the contrary, a large number of these researches have been carried out post-mortem [Scherer (127), Bockendahl and Landwehr (281), Ludwig (282), Freund and Obermayer (268), von Jaksch (283), Matthes (86), and others]. Devoto (284), Wagner (285), Limbeck (240), and Erben have vainly sought for substances of albumose-like character in blood freshly obtained from patients suffering from myelogenous leuchæmia. Strauss (273), as well as Erben (269), obtained similar negative results in cases of lymphatic leuchæmia. Von Jaksch alone found on one occasion a body of albumose character in the blood obtained by venesection from a case of myelogenous leuchæmia. Wagner (285) and von Jaksch (286) were struck by the fact that bodies of an albumose nature can be demonstrated in decomposing leuchæmic blood, as opposed to other blood, and von Limbeck (240), after allowing leuchæmic blood to stand at the ordinary room temperature for twelve hours, was able to demonstrate the presence in it of an albumose substance identical with that found by Matthes (86), although the blood had originally been free from albumoses. In view of these results, Erben undertook investigations with regard to the rôle played by autolytic processes in leuchæmic blood. As a result of these investigations, Erben was able to demonstrate the presence of both albumoses and peptone in easily detectable quantities in blood, derived from a case of myelogenous leuchæmia, which had remained in the incubator for seventy hours, although a freshly withdrawn specimen of the same blood contained no albumoses precipit-

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able by saturation with ammonium sulphate, and only doubtful traces of peptone. Additional experiments showed that the blood in splenomyelogenous leuchæmia contains a tryptic ferment, as well as traces of a peptic ferment which are not present in normal blood, and which appear to be derived from the polynuclears in leuchæmic blood. According to Erben's hypothesis (287), the leucocytes only yield this ferment as a result of their breaking down after death. Schumm (288) has also demonstrated the presence of albumins in the blood of two cases of myelogenous leuchæmia, and has further been able to determine the occurrence of a proteolytic ferment both in the blood and in the spleen (289) of a leuchæmic patient. Consequently, Schumm, notwithstanding the inconstant character of the results obtained on examination of freshly withdrawn leuchæmic blood, still holds to the view that a decomposition of protein by means of ferment may possibly occur *intra vitam*.

Another ferment has also been demonstrated by Brandenburg (290) in the polynuclears. It possesses one of the characters of ozone in turning tincture of guaiacum blue, and has also been found in the bone-marrow, not, however, in lymphatic leuchæmia [Brandenburg (290A), E. Meyer (291)].

Ellinger (157) demonstrated the protein substance originally discovered by Bence-Jones both in the blood and in ascitic fluid obtained from cases of multiple myelomata. On the other hand, Askanazy (160) found it only in the fresh extract of bone-marrow, but not in the precipitates produced by the addition of alcohol to blood, and pleural or pericardial exudates.

Von Limbeck (240) found values of 22 to 34 milligrammes for the residual nitrogen of the blood-serum in cases of chlorosis; Strauss (298) observed 21 milligrammes in pseudo-leuchæmia, 27 milligrammes in Banti's disease, and 60 milligrammes in 100 c.c. of blood-serum in myelogenic leuchæmia (298A). Landau (239) found 173 milligrammes in pernicious anæmia. Von Jaksch (299) found 64 milligrammes of urea in 100 c.c. of blood in a case of leuchæmia.

The Charcot-Leyden crystals should also be mentioned in this connection. According to investigations by Müller-Gollasch (292), by Strauss (293), and by Gumprecht (294), their colour reactions justify their classification amongst protein substances. They have also been found in blood withdrawn from cases of leuchæmia.

Conjointly with Neuberg I have sought for amino-acids in ascitic fluid obtained from a case of Banti's disease, and found a value of 0·062 per cent. Glycocoll was present in small quantities.

Too great importance should not be attached to the post-mortem detection of the occasional presence of leucin and tyrosin in leuchæmic tissues, since these substances were possibly produced as the result of putrefactive changes in those cases in which they were found. In this relation, attention may be drawn to the fact that Schumm (289) was able to demonstrate the presence of lysin, as well as small quantities of arginin, histidin, tyrosin, leucin, and ammonia as products of the autolysis of a spleen obtained from a case of acute leuchæmia.

Xanthin bodies, which are present in very small quantities in fresh normal blood [Salomon (295), von Jaksch (296)], are abundantly

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represented, and readily recognisable in the blood of cases of leuchæmia, especially after digestion in the incubator. On port-mortem examination, G. Salomon (295A) found more hypoxanthin than xanthin in the blood of two cases of leuchæmia. With the aid of the method of precipitation as silver compounds, Magnus-Levy almost invariably found hypoxanthin mixed with guanin and adenin in the blood of cases of leuchæmia, while xanthin was present only in traces.

Uric acid has been vainly looked for in normal blood and in vascular organs, yet it was found in leuchæmic blood by Körner (130) and Klemperer (297). The latter author noted 9·9 milligrammes in 100 c.c. Magnus-Levy (14) also observed considerable increase in the quantity of uric acid present in the blood, as well as in the pleural and pericardial exudates of leuchæmic patients. He found *in maximo* 22·6 milligrammes of uric acid per 100 c.c. of blood in the case of acute leuchæmia. The blood referred to appears to have been obtained post-mortem. Von Jaksch (296) met with an increase in the quantity of uric acid present in the blood of cases of severe anæmia. Weintraud (124D) found 1·9 milligrammes of uric acid in 100 c.c. of blood in a case of polycythæmia associated with enlargement of the spleen.

7. The Amounts of Sugar and Glycogen present in Blood.

Claude Bernard (163), von Mering (300), and Schenck (164), have established an increase in the quantity of sugar present in the blood of animals after blood-letting. The researches of the last author demonstrated an increase in the quantity of sugar amounting to 67 milligrammes per 100 c.c. of blood (average of six experiments). Rose (300A) also found 0·2 per cent. and more of sugar in the blood of rabbits in which hyperglycæmia had been produced as the results of blood-letting, while the quantity of sugar present in the blood of normal rabbits maintained on an abundant carbohydrate diet usually amounted to less than 0·15 per cent. According to Freund and Trinkler (301), an increase in the quantity of sugar present in the blood also occasionally occurs in anæmia secondary to carcinoma. Donati (301B) also mentions a rise in the quantity of sugar in the blood in cases of malignant tumours.

The quantity of glycogen present in the blood of cases of secondary anæmia—*e.g.*, those resulting from gastric carcinoma, severe chronic toxic conditions, as well as of cases of pernicious anæmia, chlorosis, leuchæmia, and pseudo-leuchæmia—was investigated by Gabritschewski (302), Czerny (303), Livierato (304), Kaminer (304A), L. Hofbauer (305), Sorochowitsch (306), and others, with the aid of microchemical methods. The results obtained, however, were variable, so that Sorochowitsch came to the conclusion that the reaction with iodine yielded by the leucocytes shows no feature characteristic for any given disease of the blood.

8. The Amount of Fat contained in the Blood.

The quantity of fat present in the blood as a whole was found by Erben (269, 270) to be increased in cases of chlorosis and of lymphatic leuchæmia. Freund and Obermayer (268) obtained similar results in cases

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of myelogenous leuchæmia. Rumpf (307) also obtained a strikingly high result (0·34 per cent.) in leuchæmia. The increase in leuchæmia may possibly be more or less dependent upon the breaking down of numerous leucocytes containing fat. Dawjalow (266) found 0·38 per cent. of fat in pernicious anæmia, while Erben (265) was unable to determine any abnormal increase in this disease. Rumpf (307) observed a slight rise (0·13 per cent.) in the quantity of fat in two out of three cases of pernicious anæmia. Bonniger (306A) found 1·4 per cent. in anæmia following carcinoma. Engelhardt (306B) found 0·13 and 0·28 per cent., Rumpf (307) 0·06 to 0·08 per cent., and Erben (269D) 0·52 per cent. of fat in the same condition. The values for lecithin and cholesterin are also to be regarded as relatively high in Erben's (269) cases of chlorosis and of leuchæmia, as well as in those of Freund and Obermayer (268). Erben also found a relatively large quantity of fat, lecithin, and cholesterin in the blood-serum of his cases of chlorosis and of lymphatic leuchæmia. The highest percentage of fat in the blood-serum which was observed by Erben amounted to 0·53 per cent. in a case of chlorosis. Weintraud (124C) obtained an ethereal extract containing 0·8132 per cent. of solids, 0·1229 per cent. of cholesterin, and 0·2354 per cent. of lecithin.

9. The Organic Acids of the Blood.

Scherer (127) found lactic, formic, and acetic acids in diseases of the blood, Mosler and Körner (130) formic and lactic acids, Bockendahl and H. Landwehr (281) lactic and succinic acids, Salkowski (129) formic and lactic acids, yet the majority of the investigations were carried out on blood obtained post-mortem. Lactic acid, however, is present in all blood post-mortem, as G. Salomon (308) has shown. It is also not infrequently to be found in blood freshly withdrawn from healthy individuals. Gaglio (309) and Irisawa (310) have proved the latter fact in the case of the dog, Salomon (308) and Berlinerblau (311) in the case of man.

10. Abnormal Colouring Matters of the Blood.

Syllaba found bilirubin, and in one instance hæmoglobin, in the blood-serum of seven cases of pernicious anæmia accompanied by icterus (311). Erben also found in one case of pernicious anæmia that the originally golden-yellow serum acquired after some time a beautiful green colour (265). Strauss observed bilirubin in the serum of a case of acute black-water fever which had arisen immediately after return from the tropics. These results, which Syllaba, in view of the other conditions, rightly interprets as indications of the occurrence of an erythrocytolysis, possess a special interest in connection with the fact that the same author noted an absolutely normal coloration of the blood-serum in four cases of chlorosis. The latter fact induced Syllaba to support the view that the source of the deficiency of hæmoglobin present in chlorosis is to be sought in a deficient formation of that pigment.

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11. Mineral Constituents of the Blood.

The discussion of the alkalinity of the blood is a problem of primary interest in connection with the description of the mineral constituents. This problem has entered into a new phase through the investigations of R. Höber (312), H. Friedenthal, Fraenckel, and others (313-317). The results of the physico-chemical investigations carried out by these observers have rendered it extremely probable that human blood-serum is usually either absolutely or nearly neutral in reaction. Notwithstanding this fact, some results obtained by chemical methods may be mentioned in this connection. At the same time, it must be borne in mind that the results of these researches have been obtained by means of methods of very diverse character, and consequently of different values. An exhaustive criticism of the different methods need not here be entered upon, since the whole question is still unsettled. The following examples of the methods employed by different investigators may be here adduced. F. Kraus (314) made use of the carbon dioxide method, while A. Loewy (315), myself (316), Burmin (317), and Brandenburg, have employed the process devised by Zuntz and Loewy. An acute loss of blood diminishes the alkalinity of the blood, according to Zuntz (318). Graeber (319) found normal or slightly increased alkalinity in fifteen cases of chlorosis. Peiper and others (315, 316, 320, 321) confirmed this observation. Von Jaksch (323), de Renzi (324), and S. von Moraczewski (261), are the only observers who have brought forward opposite results. The alkalinity of the blood was usually found to be diminished in severe diseases of the blood, especially in pernicious anæmia and in leuchæmia (210); yet relatively high results have been obtained in these diseases by A. Loewy and myself.

A comparative review of the investigations carried out by Erben with the aid of the same method on cases of pernicious anæmia (265), anæmia secondary to carcinoma (269D), chlorosis (270), and leuchæmia (269), gives, without doubt, the best insight into the character and amount of the total ash and of the individual mineral constituents. Strauss found 0·89 per cent. of ash (= 9·9 per cent. of the total dry residue) in a case of myelogenous leuchæmia (298A), and Coenen (269C) found 0·68 per cent. of ash in a case of anæmia following carcinoma.

Biernacki (255) notes that the amount of chlorine was found to vary from 2·27 to 3·41 per mille, that of K_2O from 0·99 to 1·59 per mille, that of Na_2O from 2·13 to 3·13 per mille, that of P_2O_5 from 4·19 to 5·52 per mille, and that of Fe_2O_3 from 0·172 to 0·898 per mille.

The tables on pp. 411, 412 give a comparative summary of the results recorded.

On reviewing the actual figures, it appears that the amount of the total ash shows in concrete cases a tendency to an increase rather than to a diminution. The large amount of chlorine present is the most striking feature which becomes manifest on considering the individual mineral constituents, and, further, the fact that Na, Ca, Mg, and SO_3 are frequently increased. On the other hand, the compounds of potassium and the phosphoric acid are frequently reduced in amount.

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TABLE A.—PARTS PER THOUSAND.

	Normal.		*Chlorosis.*				*Anæmia secondary to Carcinoma.*		*Pernicious Anæmia.*		*Lymphatic Leuchæmia.*			
	[1]	Serum (C. Schmidt).	Blood (Erben I.).	Blood (Erben II.).	Serum (Erben I.).	Serum (Erben II.).	Blood (Erben).	Serum (Erben).	Blood (Erben).	Serum (Erben).	Blood (Erben I.).	Blood (Erben II.).	Serum (Erben I.).	Serum (Erben II.).
Total ash	8·750	8·570	8·353	9·798	8·192	8·839	8·361	7·898	8·780	8·672	10·821	9·832	8·850	8·377
CO_2 ..	+	+	0·509	0·660	0·789	0·664	0·413	0·461	0·251	0·608	—	—	0·300	0·325
SO_3 ..	0·622	0·130	0·339	0·570	0·189	0·513	0·146	0·143	0·848	0·522	1·632	0·916	0·867	1·096
P_2O_5 ..	0·772	0·467	0·206	0·228	0·093	0·144	0·378	0·049	0·403	0·270	0·868	1·596	0·215	0·473
Cl ..	2·689	3·565	3·271	3·577	3·322	3·521	3·244	3·903	3·364	3·373	3·537	2·411	3·575	2·709
K_2O ..	2·523	0·382	1·352	1·625	0·924	0·643	1·430	0·026	0·767	0·571	1·850	2·071	0·522	0·509
Na_2O ..	2·109	4·638	2·798	3·284	3·233	3·834	2·808	3·970	3·440	3·769	3·424	2·550	3·783	3·209
CaO ..	0·708	0·163	0·257	0·238	0·335	0·247	0·201	0·198	0·287	0·242	0·434	0·449	0·353	0·631
MgO ..	0·046	0·036	0·049	0·055	0·054	0·065	0·045	0·026	0·068	0·071	0·050	0·044	0·039	0·035
Fe_2O_3 ..	0·714	—	0·308	0·366	—	—	0·426	—	0·110	0·005	0·092	0·338	—	—

[1] Calculated average of analyses of the total ash by Schmidt. The individual figures in this column were deduced from Jansch's percentage values with the aid of Schmidt's figures as a basis.

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TABLE B.—PARTS PER THOUSAND.

Author.	*Disease.*	*Cl.*	*Na.*	K.	*Fe.*	*Ca.*	*Mg.*	*P.*	*S.*
Schmidt, Vanach, and Biernacki[1]	—	2·673	1·654	1·487	0·551	—	—	0·326	—
Biernacki ..	Chlorosis	2·653	1·395	1·062	—	—	—	—	—
Biernacki ..	Carcinoma ventriculi	3·090	2·322	0·822	—	—	—	—	—
Freund and Obermayer ..	Leuchæmia	1·746	2·801	1·356	—	—	—	—	—
Rumpf ..	Pernicious anæmia	3·320	1·360	0·790	0·080	0·12	0·03	0·480	1·15

[1] Averages of analyses of human blood (male and female).

At an early date Becquerel and Rodier (257) noted an increase in the quantity of sodium chloride present in the blood. They found that the blood obtained by a second blood-letting was richer in sodium chloride than that obtained by the first withdrawal. Later on, a whole series of investigators—*e.g.*, von Limbeck (240), von Moraczewski (325), and others—also observed an increased amount of sodium chloride in the blood in diseased conditions. According to Rumpf (264), the quantity of chlorine may rise to such a degree that the amounts of sodium and potassium contained in the blood are insufficient to combine with all the chlorine. Remembering the results obtained in cases of hydræmia, it is natural to assume that the rise in the quantity of chlorine is to be associated with the dilution of the blood which so frequently occurs in severe cases of anæmia. The occurrence of a reduction in the quantity of potassium was emphasized by Biernacki (255), and at a later date especially by Rumpf. Since there is such a marked reduction in the quantity of potassium present in the blood as a whole in cases of pernicious anæmia, associated, however (as in other diseases of the blood), with a rise in the amount present in the serum [Erben (265)], there is much in favour of the view that the decrease in the quantity of potassium is mainly due to a reduction in the number of erythrocytes. The converse holds good with regard to the amount of sodium chloride. The quantity of sodium chloride present in the serum is generally but slightly reduced, while that in the blood as a whole is slightly increased. As the result of metabolic investigations, Erben refers the increase in the quantity of calcium and magnesium to liquefactive processes occurring in the osseous system.

A reference to the foregoing tables will show that the quantity of iron is diminished in the individual cases, since it amounts to 0·05 per cent. in the healthy individual, and is only rarely slightly diminished under normal conditions [Jolles, Hladik (328A)]. Biernacki (255) and A. Jolles (329), Jellinek and Schiffer (262), H. Rosin and S. Jellinek (330), Jolles and Winkler (180), and Mitulescu (330A), have found a more or less marked reduction in the quantity of iron present in the blood of cases of chlorosis. On the other hand, Biernacki (265) gives an account

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of six cases of chlorosis, in which he found the quantity of iron either not at all diminished or only to a slight extent. From these results, he draws the conclusion that the characteristic feature of chlorosis is not the reduction in the amount of hæmoglobin, but rather the diminution in the amount of iron contained in the red blood-corpuscles. The justification for this conclusion has been contested by von Noorden (76), and recently also by Erben (270). After von Seiller (330B) had deducted the quantity of iron derived from hæmoglobin, he still found 0·0232 per cent. of iron existing in the form of a nucleo-proteid present in the blood-clot obtained from two cases of chlorosis. He only found minute traces of the latter substance in another instance. The foregoing authors have also found a more or less distinct decrease in the quantity of iron present in the blood of cases belonging to the different forms of secondary anæmia. Jolles and Winkler, Rosin and Jellinek, and Mayer, made similar observations in the case of leuchæmia, and Erben, Rumpf, Rosin, and Jellinek obtained similar results in pernicious anæmia. According to Biernacki, the diminution in the quantity of iron present in the blood in disease is not so great as the reduction in the quantity of potassium. Further, the observations made by the latter author, as well as the similar observations of Jolles, Jellinek, Rosin and Jellinek, Erben, Mitulescu (330A), and others, appear to indicate that a complete parallelism does not exist between the quantity of iron and that of hæmoglobin in the blood. Text-books of hæmatology may be referred to for details with regard to the latter quantity.

Although normal blood-serum contains no iron, Jolles (329) has occasionally, yet not constantly, found traces in the blood-serum of cases of severe anæmia, and Erben (265) has found 0·005 per cent. Fe_2O_3 in pernicious anæmia. Both investigators failed to find iron in the blood-serum of chlorotic and leuchæmic patients.

According to Mayer's investigations (181), the reduction in the quantity of iron present in the blood in cases of chlorosis, anæmia, and leuchæmia appears to run parallel with a rise in the quantity of iron present in the urine.

It is necessary to consider not only the iron present in the blood and in the urine, but also that stored in the tissues, in order to obtain an insight into the metabolism of iron in diseases of the blood. Since, however, some other alterations in the tissues are to be found in diseases of the blood, a brief summary of the tissue changes which occur during diseases of the blood may here be given. The blood itself has also, to some extent justifiably, been termed a tissue. Consequently, certain other properties of the cellular elements of the blood may be discussed in this connection.

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B.—CHEMISTRY OF THE ERYTHROCYTES AND TISSUES OF THE ORGANISM.

1. Physical and Chemical Characteristics of the Erythrocytes.

Herz (331), Daland (332), and Friedheim (333), and at a later date Biernacki (225) and von Limbeck (240), have found that the size of the erythrocytes is increased in severe types of anæmia. At the same time the relative weight of the erythrocytes as compared with that of the plasma was found to be reduced to one-fourth of the normal value in two cases of severe anæmia investigated by Krüger (260). Erben (269D) found a decrease amounting to one-half of the normal in anæmia due to carcinoma, and Erben (265) and Sawjalow (266) observed an almost equally great diminution in pernicious anæmia.

Erben (270) also found that the weight of the erythrocytes was reduced to nearly one-half of the normal in chlorosis and in lymphatic leuchæmia. Kossler ascertained that the blood-corpuscles were reduced in size in some instances to a very considerable extent in cases of chlorosis and of secondary anæmia (238).

Since the number of erythrocytes was reduced to one-tenth, and their weight to one-third to one-fourth of the normal, in a case of pernicious anæmia investigated by Erben, it may be calculated that the average weight of a single red blood-corpuscle amounted in this case to about two and a half times that of a normal erythrocyte. A similar conclusion, however, can scarcely be drawn from the results obtained by Sawjalow and Kössler in cases of a corresponding nature. The dry residue of the erythrocytes amounted to about two-thirds of the normal in Erben's case, whereas it was somewhat higher than normal in that of Sawjalow. The amount of the dry residue of the erythrocytes was absolutely normal in the case of anæmia due to carcinoma which was investigated by Erben (269D).

Von Jaksch (336) found that the quantity of nitrogen contained in the erythrocytes in cases of secondary anæmia, as well as of chlorosis and of leuchæmia, was, it is true, not invariably, but still very frequently, diminished. On the other hand, he failed to find such a decrease in pernicious anæmia. Hoke at a later date made nearly the same observation when working in von Jaksch's clinique (337). Kossler (238) also obtained similar results in chlorosis. Erben (265), however, found that the total quantity of protein contained in the erythrocytes in pernicious anæmia was reduced to somewhat less than two-thirds of the normal, while the amount of protein contained in each erythrocyte was more than one and a half times as great as normal. The quantity of protein contained in the erythrocytes was also diminished in Sawjalow's case of pernicious anæmia. The amount of protein was normal in Erben's case (269D) of anæmia following carcinoma.

Erben noted that the amount of fat and lecithin present in the erythrocytes was increased in pernicious anæmia (265), but not in the cases of chlorosis. Sawjalow (266) also found a relatively large amount

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of fat in the erythrocytes of a case of pernicious anæmia. Erben (269D) observed 0·42 per cent. of lecithin in anæmia secondary to carcinoma.

The total ash of the erythrocytes, the normal value of which has been determined by Schmidt as 0·828 per cent., amounted to 0·89 per cent. in a case of pernicious anæmia investigated by Erben (265), to 0·62 per cent. in a case of anæmia due to bothriocephalus examined by Sawjalow, to 0·854 to 1·297 per cent. in the cases of chlorosis examined by Erben, to 0·95 per cent. in Erben's case of anæmia due to carcinoma, and to 1·69 per cent. in the latter author's case of lymphatic leuchæmia (269).

The quantities of Cl, K_2O, Na_2O, and of Fe_2O_3 present in the ash are of primary importance. Biernacki (255) found from 0·315 to 0·361 per cent. of chlorine in chlorosis, as well as in secondary anæmias. The corresponding values for the healthy individual vary from 0·292 to 0·298 per cent. Erben found 0·331 per cent. of chlorine in his case of pernicious anæmia (265), 0·170 per cent. in his case of anæmia resulting from carcinoma, 0·316 to 0·384 per cent. in his cases of chlorosis (270), and 0·136 per cent. Cl in his case of lymphatic leuchæmia.

The results of Biernacki's estimations of the quantity of K_2O were very variable (0·120 to 0·244 per cent.), but were usually lower than the normal value of 0·243 to 0·252 per cent. determined by the same author. The quantity of K_2O amounted to 0·242 per cent. in Erben's case of pernicious anæmia, to 0·48 per cent. in his case of anæmia following carcinoma (269D), to 0·274 to 0·524 per cent. in his cases of chlorosis, and to 0·775 per cent. in his case of lymphatic leuchæmia.

Erben found 0·072 per cent. of Na_2O in pernicious anæmia, 0·001 per cent. in anæmia following carcinoma, 0·144 and 0·139 per cent. in chlorosis, and 0·019 in lymphatic leuchæmia.

Biernacki found that the quantity of Fe_2O_3 was diminished in only one case of gastric ulcer and in one case of chlorosis; while the results obtained in other cases of chlorosis and secondary anæmia were either normal or only slightly higher than normal. The same statement holds good with regard to Erben's results. He found 0·099 per cent. of Fe_2O_3 in pernicious anæmia, 0·144 per cent. in anæmia following carcinoma, 0·130 to 0·167 per cent. in chlorosis, and 0·16 per cent. in lymphatic leuchæmia.

The question of the oxygen capacity of the blood is of interest in the present connection for the following reasons: (1) Because several observers [Bohr (345), Abrahamson (346), Haldane (347), Tobiesen (348)] have expressed the view that there are different compounds of hæmoglobin with oxygen combined with different proportions of that gas; (2) because Biernacki (255) has found that the quantity of oxygen yielded *in vacuo* by blood previously saturated with that gas varies little in cases in which the amount of hæmoglobin is greatly reduced from that obtained under normal conditions; and, lastly, because Lorrain Smith has found that the percentage oxygen capacity of the blood is reduced in chlorosis, while the total oxygen capacity remains unaltered. Lorrain Smith also states that both the percentage and the total oxygen capacity of the blood are reduced in pernicious anæmia (349). The results

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obtained in his investigations of anæmia by the carbon monoxide method are summarized in the following table :

	Total Oxygen Capacity of the Blood in c.c.	*Total Volume of the Blood in c.c.*	*Red Corpuscles in Millions per c-mm.*	*C.c. of Blood per 100 Grammes Body-weight.*	*C.c. of Oxygen Capacity per 100 Grammes Body-weight.*
Normal males	599	3,254	—	4·6	0·83
Normal females	533	3,138	—	5·3	0·92
Cases of chlorosis with hæmoglobin averaging 39·9 per cent.	359	4,883	3·222	10·8	0·79
Cases of chlorosis with hæmoglobin averaging 68 per cent.	387	3,113	3·920	6·4	0·79
Cases of pernicious anæmia with hæmoglobin averaging 26·5 per cent... ..	210	4,529	0·949	8·6	0·40
Cases of anæmia from hæmorrhage	220	3,926	3·067	6·5	0·39

This table includes the observations on normal males, the results of which are given in the original paper describing the carbon monoxide method (380). When the results from cases of chlorosis are examined, it is clear that the blood of these patients has a practically normal oxygen capacity of 0·79 c.c. per 100 grammes of body-weight. This is possible only if they have a normal amount of hæmoglobin ; and as they have in all cases a marked decrease in the percentage of hæmoglobin per c.c. of blood, the inference is that the plasma is increased. In other words, chlorosis is not a true anæmia in the sense that there is a loss of hæmoglobin. From this result flow important conclusions regarding the various phenomena observed in cases of chlorosis.

In pernicious anæmia, on the other hand, there is a markedly decreased oxygen capacity of 0·40 c.c. per 100 grammes of the body-weight. This corresponds to the fact so prominently brought out at post-mortem examinations of cases of this disease—viz., that the liver and other organs are loaded with hæmosiderin derived from disintegrated hæmoglobin. The plasma is, on the average, above normal in these cases, but in one case which was examined eight times during a period of seven months, it was noted that the volume of plasma varied from 7·6 c.c. per 100 grammes of body-weight to 3·6 c.c. In a given case, therefore, the severity of the condition, which depends essentially on the destruction of the blood, may be marked by an increase, or decrease, of the volume of plasma.

Finally, the same method applied to the anæmia of hæmorrhage shows that the oxygen capacity is decreased, as in pernicious anæmia, and that in the cases examined the volume of plasma was moderately increased, averaging 6·5 c.c. per 100 grammes of body-weight (381).

For a comparison of the results of Welcker's method of estimating the volume of the blood in animals with the carbon monoxide method, *vide* Gordon Douglas (382).

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Kraus, in investigations carried out conjointly with his assistants Kössler and Scholz, finds that hæmoglobin combines with the same proportion of oxygen in anæmic individuals as in healthy ones. The quantities of oxygen required for complete saturation were abnormally high in only two cases, in which the quantity of hæmoglobin was extremely reduced (350). In the meantime, S. Mohr (350A) has obtained results similar to those of Kraus, and has suggested that the fulfilment of the oxygen requirements of anæmic persons is rendered possible in part by the foregoing means, and in part owing to an improved utilization of oxygen, as well as to an increase in the velocity of the blood-flow associated with a rise in the systolic output of the heart.

The catalytic power of decomposing hydrogen peroxide possessed by the blood, which appears to be more or less nearly related to the number of erythrocytes, or to the quantity of hæmoglobin, has been investigated in cases of anæmia by Jolles (352A), Silbergleit and Morse (353). The former author sometimes found a diminution of catalytic power in carcinoma and in tuberculosis, while the two latter obtained normal results in two cases of carcinoma. Cases of chlorosis and of myelogenous leuchæmia were also investigated by Silbergleit and Morse, but the material at present available does not suffice for the formation of definite conclusions.

2. Physical and Chemical Characters of the Tissues of the Body.

As the result of investigations of the dry residue of different tissues, Rumpf and Dennstedt (334) found that there was scarcely any alteration in the dry residue of the heart in pernicious anæmia, while that of the liver and of the brain was slightly greater than normal. On the other hand, von Moraczewski (335) was able to demonstrate a diminution of the dry residue of the heart in pernicious anæmia, as well as in anæmia following carcinoma.

Von Moraczewski (335) found an accumulation of chlorine and phosphorus in the organs. Rumpf (334) also found in his case a rise in the quantity of chlorine present in the heart, liver, spleen, and brain. The quantity of P_2O_5 present in the heart and liver was practically normal, while that present in the spleen and in the brain was much above normal.

The quantity of iron present in the organs has been studied by Quincke and others (55, 272, 338-344). Quincke found that the quantity of iron deposited in the organs of dogs after repeated artificial withdrawals of blood was either abnormally small or completely absent, while after transfusion of blood he was able to demonstrate the presence in the liver, spleen, and bone-marrow of an abnormally large number of granules containing iron. The theoretical significance of these results with regard to current views upon the pathogenesis of different forms of anæmia is obvious.

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APPENDIX.

The Toxicity and Hæmolytic Action of the Blood-Serum.

The toxicity of the blood-serum in pernicious anæmia was experimentally tested on animals by Strauss and Bloch (60, 61). Kühnau carried out similar experiments with leuchæmic blood (137). Strauss injected into a rabbit every two days for a period of twelve days 2 c.c. of blood-serum obtained from a case of pernicious anæmia, with the result that not the slightest sign of toxic phenomena was to be observed. Bloch likewise injected into mice and guinea-pigs, both subcutaneously and intravenously, blood-serum derived from a case of pernicious anæmia, with negative results. He found only in the case of the guinea-pigs a striking eosinophilia during the first days of the investigation. After intraperitoneal injection of 50 c.c. of leuchæmic serum into a dog weighing 12 kilogrammes, Kühnau found a considerable increase in the number of leucocytes and in the quantity of uric acid present in the urine. From his results, it appears that the serum did not produce any other distinct effects.

The hæmolytic power of the blood-serum in diseases of the blood has been tested by different authors since Maragliano carried out the first researches in this field. The different investigators, however, employed different methods. Ascoli, Eisenberg, Kreibich, and others, tested the hæmolytic action of human blood-serum upon human blood-corpuscles (isolysis) (355-357), while Halpern, Hedinger, Schupfer and de Rossi (358, 359) (41), and others have examined the hæmolytic action of human blood-serum on the red blood-corpuscles of rabbits. Of the first-named observers, Kreibich has in no case found hæmolysins, and Ascoli has only found them in anæmia following carcinoma. Eisenberg (356) obtained positive results in single cases of the following diseases: pernicious anæmia, carcinoma recti, marasmus, tuberculosis, hæmophilia, and malignant lymphoma. Donati also found iso-agglutinins more frequently in different forms of anæmia than under normal conditions (360). Halpern found that the hæmolytic action of blood-serum on rabbits' blood was not increased either in pernicious anæmia or in morbus maculosus [Werlhofi (358)]. On the other hand, Schupfer and de Rossi found a rise of hæmolytic power in the case of anæmia due to anchylostoma (41). Erben failed to find auto- and isolysins in two severe cases of scurvy associated with secondary anæmia and urobilinuria (361). Strauss was unable to demonstrate any increased hæmolytic power in anæmia splenica (362). Michaelis and Kober have regarded autolysins as responsible for many cases of hæmoglobinuria (363, 364), and Donati and Landsteiner (364A) have carried out investigations with the view of throwing light on this problem. Bard found that hæmorrhagic serous exudates in patients suffering from cancer have a hæmolytic action, while this is not the case as regards purely serous exudates (365). Further, Micheli and Donati ascertained that extracts of carcinomata and also of sarcomata sometimes possess a hæmolytic action (366). Kullmann's numerous researches have proved the same point as

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regards carcinoma (367). A whole series of investigators [recently von Wunschheim (368) and others] have shown that different forms of bacteria possess hæmolytic properties. These results were also to be foreseen in view of purely clinical observations. For example, it is well known that not only severe forms of anæmia, but also cases of actual hæmoglobinuria, occur as a result of acute infective diseases [cases of Heubner (369), Immerman (370), H. Finkelstein (271), Grawitz (141), and others, as well as the typical cases of black-water fever following malaria, for which I am inclined to regard an endogenous toxic action, more or less closely connected with the malarial infection, as responsible]. Isaak and van den Velden have produced a precipitate in the blood-serum of a patient suffering from bothriocephalus anæmia by means of an extract obtained from the worm itself, and have obtained specific precipitins in rabbits which had been previously treated with a substance obtained from the proglottides of the worm. Numerous other facts have been brought to light as a result of strenuous investigation in the field of the hæmolysins and precipitins, but a fuller review of this subject would exceed the limits of this section.

The fact that therapeutic investigations have been carried out with the blood-serum of anæmic patients, with the object of stimulating the formation of blood-corpuscles, follows as a consequence not only of the present trend of research, but also of the circumstance that the therapeutics of the diseases of the blood has not kept pace with the great advances made in hæmatology owing to the introduction of new methods of investigation. C. S. Engel (373) has been especially prominent in the carrying out of such investigations. He sought to produce active antibodies in rabbits which he had previously treated with the blood-serum of patients suffering from carcinomata. Courmont (374) tried another method. He tried to stimulate the formation of blood by the injection of minimal doses of the blood-serum of goats, which normally has a slight hæmolytic action. Lucatello and Malon's (375) research was carried out on opposite lines. They endeavoured to obtain favourable results in cases of leuchæmia by destroying the white blood-corpuscles by means of a leucolytic serum obtained from rabbits and sheep which had been previously treated by the repeated injection of leucocytic extracts. It would lead us too far here to attempt a full discussion of the action of Röntgen rays upon the blood-forming organs and the blood itself [R. Heinecke (376), H. Milchner and M. Mosse (377)],[1] and it is only possible to refer to the fact that Linser and Helber (378)[2] have succeeded in producing a leucotoxic substance in blood-serum as the result of exposure to Röntgen rays. An exhaustive discussion of this problem must also be avoided in this connection, since this would not only far exceed the limits of a description of metabolism in diseases of the blood, but also involves a question the investigation of which is still only in its initial stages.

[1] Renon: La Sem. Méd., Nov., 1905.

[2] Curschmann and Gaupp: Münch. Med. Wochenschr., Nr. 50, 1905. The leucotoxin which appears in the blood of leuchæmic patients after treatment with Röntgen rays selectively destroys the leucocytes, both in the circulation and *in vitro*. The toxine is destroyed by exposure to a temperature of 60° C. for half an hour.

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Hæmophilia addendum by J. A. Milroy, M.A., M.D.

Hæmophilia is a hereditary congenital disease of the blood, characterized by the tendency to excessive hæmorrhages from the slightest wounds—*e.g.*, extraction of teeth, etc. It almost invariably affects only the male members of a family, but transmission occurs through the female line. The individuals affected are usually in normal health, with the exception of the diminished coagulability of their blood.

The blood of hæmophilic individuals coagulates more slowly outside the body than that of normal individuals. The time necessary for coagulation is shortened by the addition of a trace of normal human defibrinated blood. On analysis, the hæmophilic blood is found to contain all the known constituents necessary for coagulation. It contains sufficient fibrinogen, sufficient calcium salts, and apparently a normal amount of the zymogen of fibrin ferment. The only constituent necessary for coagulation which appears to be deficient in amount is the substance ("kinase") which converts the zymogen of fibrin ferment into enzyme. In some cases of hæmophilia the profuse hæmorrhages are limited to certain vascular areas—*e.g.*, to the mucous membranes; while in other regions in which vascularity is a marked feature—*e.g.*, the skin—normal conditions prevail. This fact is partly to be explained by thinness of the vessel walls in the areas affected; structural defects of the vessel walls, however, can only explain the liability to hæmorrhages: they do not account for the uncontrollable character of the bleeding.

The most characteristic features of the hæmorrhages occurring in hæmophilia are that the clot formed at the opening in the vessel is very loose in character, and does not adhere firmly to the vessel wall, and that the blood consequently trickles through the imperfect clot in a continuous stream. These facts suggest that under normal conditions the injured vessel wall forms one or more substances, which aid the the process of coagulation. It has been suggested by Abderhalden that this substance is a kinase, which converts the inactive zymogen of fibrin ferment into the active enzyme. It is possible, however, that there may be different types of hæmophilia, in which the absence of other constituents than kinase may be involved. The greater part of the literature of the subject may be obtained from the references contained in the subjoined list of papers on hæmophilia.

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CHAPTER VIII

DISEASES OF THE KIDNEYS

By CARL von NOORDEN.

Translated by F. H. Edgeworth, D.Sc., M.B., B.C.

I.—THE INFLUENCE OF RENAL DISEASE ON METABOLISM.

The degree of oxidation in nephritis was first determined by Hanover in the following case: The patient, who suffered from granular kidney, exhaled 0·142 gramme C. per kilogramme body-weight per minute, the normal amount, according to the same authority, being 0·137 gramme—an almost identical quantity. Salomon's estimate of the consumption of oxygen, obtained when the patient was fasting and completely at rest, is more reliable (*cf.* Minimal Metabolism). The girl, who was twenty-six years of age, and suffering from chronic nephritis, without œdema, consumed between 3·88 and 4·00 c.c. O_2 (per kilogramme per minute, mean of twenty-two observations). These figures are normal, taking into consideration her size and state of nutrition. In uncomplicated cases of nephritis the state of nutrition often remains unaffected, but there are many and various factors to be taken into account which may lead to its impairment. Gastric and intestinal disturbances, often of a serious nature, are frequently present in acute nephritis, and these in course of time may damage the assimilative powers. In such cases vomiting and diarrhœa are indicative of uræmia. If the initial violent symptoms can be overcome, the difficulty of ensuring a sufficient supply of nutriment is not a very serious one, and the patients recover without any great loss of weight.

In cases of chronic parenchymatous nephritis, periods occur when the patient's condition becomes very distressing, as a result of increasing œdema. Food is utterly distasteful, and if taken in any quantity produces vomiting. This may occur only occasionally, or over a protracted period of time. In the long intervals of improvement so characteristic of this variable disease the patient's health is so much restored that, where a final recovery takes place, the tissues will be found to have suffered no serious damage.

Wasting is still less characteristic of the granular kidney. Nutrition remains excellent for many years, and the appetite is generally so good that patients, in accordance with their old habits, may be disposed to excess in eating and drinking. One meets many people suffering from

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renal cirrhosis who are quite stout. It is only when the general health begins to be seriously affected that the assimilative powers become impaired. This is especially the case where chronic uræmia, with headache, nausea, vomiting, and apparently unaccountable diarrhœa is developed. The physical condition of the patient becomes rapidly worse. Wasting occurs as a result of continued insufficient assimilation, especially in those who suffer from the disease in early life. I cannot conceal the fact that, in my experience, the monotonous diet often ordered in these cases promotes the wasting. The exclusion of all stimulants, the prohibition of red meat, the insistence on a milk diet, lead to loss of appetite and malnutrition. The patients often improve with surprising rapidity when the food is changed [von Noorden (2)].

II.—PROTEIN METABOLISM IN NEPHRITIS.

It is difficult to show whether the metabolism of protein follows the same laws in nephritis as in health—that is to say, whether it is determined exclusively by the nature of the diet and the state of nutrition. Every experiment presupposes that the total amount of nitrogen excreted in the urine and fæces comes from the proteins of the blood. Experimentally, this is not always the case in nephritis. A new and dominant factor is introduced—namely, the excretive capacity of the kidneys. It is well known what alterations are produced by such changes of capacity, especially as regards the urine. Analysis shows similar variations in the amount of nitrogen, as well as in other constituents of the urine (see below). For instance, if less nitrogen is found in the urine than corresponds to the nature of the diet, one cannot be sure whether it is to be accounted for by a diminution of proteid metabolism or by the retention of the products of such metabolism. If more nitrogen is found, it still remains doubtful whether an abnormal increase of proteid metabolism is taking place, or whether the kidneys are discharging from the body an increased amount of urea, previously formed and stored up. Nothing in the general health enables one to guess whether the excretory powers are in a good or bad condition [von Noorden and A. Ritter, von Rzetkowski, G. Ascoli (3), etc.]. In cases where prolonged observation has eliminated every possibility of error, one cannot bring forward the slightest support for the view that the proteins of the body suffer, either in renal cirrhosis or in chronic parenchymatous nephritis [R. Fleischer, von Noorden, L. Mohr and M. Kaufmann, J. A. Butler and H. S. French (4)]. I append the results of observations, extending over two months and longer, of the intake and output of nitrogen in parenchymatous nephritis. In these cases the output was certainly subject to considerable variation, but the total nitrogen balance, on a diet sufficient for the needs of the body, was in the patient's favour.

In this case the girl, aged sixteen, and suffering from parenchymatous nephritis, with slight œdema, ingested in the course of fifty-two days 416 grammes nitrogen, and excreted in the urine 351 grammes nitrogen.

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The energy value of the food was 30 to 35 calories per kilogramme per day. Examination showed that the fæces never contained more than 1 gramme nitrogen daily, so that, in spite of a small intake of albumin, the patient fully maintained her nitrogenous balance. The experiments of Ernberg (4A), who gave his patients an unusually small amount of protein, also militate against the theory of any pathological increase of protein metabolism.

On the other hand, it would appear that qualitative changes in the proteins occur in chronic nephritis. Erben found in parenchymatous nephritis a relative, and practically an absolute, increase of globulin in the blood, whilst the serum albumin was invariably diminished. He explains this teleologically. The fluids enrich themselves with globulin because it is less diffusible and less easily secreted by the kidneys. The opposite theory might be equally well maintained—viz., that the plasma becomes richer in globulin because relatively less is secreted by the kidneys.

Although it is hard to bring forward definite proof, it seems very probable that in acute uræmia poisons circulate in the organism which damage the cells, destroy the protoplasm, and so allow the number of nitrogenous extractives to increase, just as happens in fever, phosphorus-poisoning, etc. Richter thinks that an observation of his demonstrates this, though to me the proof does not appear entirely convincing (6). In one case, however, which I saw this explanation was the obvious one.

A boy, aged eleven years, developed acute nephritis in the third week of a mild attack of scarlet fever. From the onset of the illness he took daily 1,500 c.c. of milk and 100 grammes of cane-sugar dissolved in ½ litre of water. He took this quite regularly, with the exception of the third and fourth days of the illness, when uræmic symptoms appeared which made the taking of any food impossible. As these indications diminished, he reverted on the fifth day to the former régime.

Day.	*Urine.*	*Nitrogen.*	*Albumin.*	*Fæcal Nitrogen.*
	c.c.	Gm.		Gm. per Day.
1	200	3·4	Much	
2	180	3·3	,,	
3	120	1·9	,,	
4	190	2·5	,,	
5	450	5·6	,,	
6	1,300	8·2	,,	
7	2,100	15·6	Small amount	1·55
8	2,900	20·2	Trace	
9	1,550	16·1	,,	
10	1,600	8·2	None	
11	1,600	6·9	,,	
12	1,700	5·7	,,	
13	1,650	4·8	,,	

The diet contained about 7·8 grammes of nitrogen per day. On the first three days 23·4 grammes of nitrogen were ingested; on the two days when the patient fasted the proteid metabolism may be calculated, when normal, as being at the outside 8 grammes. The total of about 39·4 grammes which should appear in the urine and fæces amounted on these five days to 23·2 grammes only (deficit = 16·2 grammes).

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On the ensuing five days 39 grammes nitrogen were ingested, but in the excreta 76 grammes were found—that is, an excess of 37 grammes. If the 16·2 grammes retained during the first to fifth days are deducted from the 37 grammes, it appears that the patient, although not feverish, lost 20·8 grammes nitrogen. This heavy loss is not to be attributed to the nature of the diet, but solely to the disease. In the following days (eleventh to thirteenth) the nitrogenous excretion lessened, and equilibrium was restored, as is the rule with convalescents.

This, so far, is the only available investigation which clearly demonstrates that the uræmic intoxication during the course of nephritis may lead to increased breaking down of protein.

III.—THE INFLUENCE OF RENAL DISEASES ON THE DIGESTIVE ORGANS.

The occurrence of serious gastric and intestinal disturbances during the course of nephritis has already been mentioned. These frequently assume so important a character that the patients are thought to be suffering primarily from gastric trouble, and the thought of nephritis does not occur to the superficial observer. A train of symptoms is developed which closely resemble a violent attack of gastric catarrh or gastro-enteritis. This is to be attributed partly to œdematous alterations in the mucous membrane [C. Bartels (7)], partly to the influence of the uræmic condition of the nervous system [Leube (8)]. Although the latter explanation fully accounts for many of the symptoms, yet others (such as uræmic intestinal ulceration) must be attributed to toxic chemical action. As a matter of fact, proof is forthcoming that, in cases of anuria, substances usually got rid of by the kidneys are secreted into the alimentary tract (see below). Of these, the most irritating chemically is ammonia, which is formed in the intestines by decomposition of the secreted urea [A. Hirschler, J. Fischer, Senator, G. Ascoli (9)]. It is also noticeable that the fæces in uræmic diarrhœa are extremely rich in ammonia (see below).

1. The Saliva.

Jawein states that in four patients suffering from chronic nephritis the amount of saliva was lessened and its diastatic ferment diminished. Although daily observations often show a decrease of the saliva, yet the exceptions are too numerous to permit of a generalization to that effect. My own experience shows that this is also true of the diastatic ferment. On the other hand, ptyalism and stomatitis may occur amongst the symptoms of uræmia. Barié attributes such conditions to the retention and poisonous action of a body, not as yet identified, which irritates the salivary glands. Patients suffering from renal disease react to pilo-

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carpin with marked ptyalism (11). Leube makes use of this fact as a means of reducing the œdema more rapidly (12).

In my experience the saliva of renal subjects often, though not invariably, yields a negative or only very slight sulphocyanide reaction. My former assistant, M. Dapper (13), who, at my request, made systematic observations, has been able to confirm this, though he could not discover any constant relation between its presence and the nature or severity of the disease.

Of pathological excreta, *urea* must first be mentioned. Its presence in the saliva was first demonstrated by von Pettenkofer (14). Subsequent investigations showed that the amount of urea secreted by renal patients in the saliva is not great [R. Fleischer, von Zezschwitz, von Noorden, and A. Ritter (15)] — in fact, it is frequently quite absent [R. Fleckseder (15)]. Fleischer states the greatest daily amount to be 0·3 to 0·4 gramme of urea (under the influence of pilocarpin). In forty-five cases of nephritis urea was present thirty-eight times. Of these, it was invariably found in cases of renal cirrhosis and in uræmia (16). I should estimate the excretion of nitrogenous derivatives in the saliva somewhat more highly than Fleischer did as the result of his estimations of urea. We have frequently demonstrated the presence in the saliva (in cases of renal cirrhosis and parenchymatous nephritis) of 0·4 to 0·5 gramme nitrogen. In these cases the saliva was secreted two to three hours after an injection of pilocarpin.

Boucheron was the first to describe the presence of *uric acid* in the saliva as well as in the secretions of the nose, pharynx, and bronchi of uræmic patients. According to his later paper (18), uric acid is only present between meals, and is not secreted by the salivary glands during mastication. Galippe and Fleckseder erroneously dispute its presence in the saliva (15, 18). Though I have often failed, yet in some cases I have found a murexide reaction in the saliva of uræmic patients after the administration of pilocarpin (Ludwig-Salkowski method).

Strauss investigated the *molecular concentration* of the saliva in cases of renal disease under Cohn (19). The lowering of the freezing-point (−0·18° to 0·29°) was within the normal limits (−0·07° to 0·34°).

2. Gastric Digestion.

Biernacki has investigated the gastric digestion of renal patients. The secretion of *hydrochloric acid* and the production of *rennin* and *pepsin* were very considerably diminished when the disease was at its height —*i.e.*, in acute and chronic nephritis with œdema, and in the acute relapses of interstitial nephritis. The food passed from the stomach into the intestines without any abnormal delay. Von Jaksch also notes a deficiency of hydrochloric acid in nephritis (20). I cannot admit, however, that this is invariably the case. In four out of nine patients suffering from acute nephritis an excess of hydrochloric acid was present at the usual interval after meals [von Noorden (21)]. The results obtained by Krawkow are even more unlike those of Biernacki. In twenty-six cases of diffuse nephritis hydrochloric acid was never absent, and was

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only diminished in eight cases (22). Zipkin records similar results (23). My assistant, M. Dapper, investigated the gastric digestion in fifteen renal cases. In three of these free hydrochloric acid was absent; in seven it was diminished (less than 20 c.c. of decinormal alkali to 100 c.c. of gastric juice); in the remaining cases it was normal. Without ascribing too much importance to it, I may also quote the observation of Bernard and Barreswil that nephrectomized dogs do not cease secreting an active gastric juice (24). I am in entire agreement with Biernacki as regards the motor manifestations of the organ.

Although Vierhuff demonstrated the cessation of all gastric secretions in a case of renal cirrhosis, and at the autopsy found atrophy of the mucous membrane, this was an accidental complication, and in view of the evidence cited above, cannot be regarded as dependent upon the nephritis (25). Wagner also mentions that amongst twenty-six patients suffering from achylia gastrica, three were the subjects of chronic nephritis.

Urea.

It is doubtful whether urea is swallowed with the saliva or secreted by the gastric mucous membrane. I have not myself been able to prove satisfactorily the presence of urea in food vomited or withdrawn from the stomach, although in the same cases it was certainly present in the saliva. On the other hand, I can confirm the results of Leos, who found as much as 0·017 per cent. of *ammonia* in the gastric contents of uræmic patients (25A).

3. Absorption and Fæces.

The thorough investigation of the fæces in renal disease was first undertaken by von Noorden and A. Ritter (3), although isolated results had previously been recorded [Fleischer (4), P. Müller, J. Prior (26)]. Since then many fresh statistics have been published—at all events, as regards the secretion of nitrogen (27). The absorption of fats, where proof could be obtained, left nothing to be desired [von Noorden and Ritter (3)]. The excretion of nitrogenous substances was less satisfactory. In the majority of the cases investigated the loss of nitrogenous matter was certainly greater than normal, both as regards its absolute amount and relatively to the nitrogen of the food. On the other hand, von Noorden and Ritter found in patients without uræmia, suffering partly from interstitial, partly from acute or chronic parenchymatous nephritis, an abnormally high percentage of nitrogen in the fæces. Diarrhœa was not present. The excretion of nitrogen varied considerably in individual cases without any corresponding change in diet, in the nature of the stools, or in the general condition. As there was no corresponding variation in the dry substances, and especially none in the fats, it must be concluded that the increase of nitrogen in the urine and fæces is due, not to impaired absorption, but to the vicarious secretion of extractives stored up in the organism. The following table, in which I give only those cases with an excess of nitrogen in the fæces, shows that

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such loss—through the intestines—may be very considerable, and may form a large proportion of the total amount excreted :

Disease.	*Food Nitrogen (Average).*	*Fæces Nitrogen (Average).*	*Fæces Nitrogen.*	*Author.*
	Gm.	Gm.	Per Cent. of Food N.	
Chronic nephritis.. ..	14·13	1·97	13·9	Müller (26)
Chronic nephritis.. ..	8·23	1·17	14·2	,,
Amyloid nephritis ..	15·86	1·98	12·5	Kornblunn (28)
Chronic nephritis.. ..	10·00	2·37	23·7	Mann (28)
Granular kidney	20·84	2·06	10·0	,,
Amyloid kidney	20·11	2·10	10·5	,,
Granular kidney	17·70	2·88	16·3	Noorden and Ritter (3)
Granular kidney	12·30	1·76	14·3	,, ,,
Parenchymatous nephritis	11·00	1·86	16·9	,, ,,
Parenchymatous nephritis (same case)	10·70	1·32	12·3	,, ,,
Parenchymatous nephritis (same case)	15·60	2·43	15·6	,, ,,
Parenchymatous nephritis (same case)	18·70	3·07	16·4	,, ,,
Acute nephritis	13·80	1·48	10·7	,, ,,
Granular kidney	20·70	3·31	16·0	Strauss (19)
Parenchymatous nephritis	20·06	5·61	27·8	Ascoli and Licci (27)
Parenchymatous nephritis (same case)	17·16	5·59	32·5	,, ,,
Parenchymatous nephritis	17·90	1·93	10·8	,, ,,
Acute nephritis	6·27	1·67	26·6	,, ,,
Granular kidney	19·30	2·70	14·0	Mohr and Dapper (27)
Parenchymatous nephritis	9·76	1·29	13·2	Butler and French (4)
Parenchymatous nephritis (same case)	6·14	1·00	16·2	,, ,,
Acute scarlatinal nephritis	7·80	2·03	26·0	Von Noorden

Equally high figures are, I believe, to be found in the works of Rudenko, Korkounow, Evdokimow, Garnie, and Grigoriew (29), but I have not been able to see their original papers. In many other cases normal amounts are quoted [*cf.* the exhaustive Table I. of G. Ascoli (3)]. The increased quantity of nitrogen is not allied to any special form of nephritis or to the occurrence of uræmia. In fact, the largest amount excreted—more than 3 grammes of nitrogen daily—is only present, as my more recent investigations show, in cases where diarrhœa occurs (uræmic diarrhœa, amyloid degeneration of the kidneys and intestines). In such cases the daily evacuations frequently contained 5 to 6 grammes nitrogen. It is obviously important, where the loss of nitrogen through the fæces is considerable, to inquire further into the nature of the substances excreted. So far very little is known. Investigations commenced in my laboratory have not yet been completed, and so far only one result is certain—*i.e.*, that an unusually large amount of ammonia salts is often present in the diarrhœic stools of uræmia. It may frequently constitute from 10 to 20 per cent. or more of the total fæcal nitrogen. In cases of acute diarrhœa, with no kidney affection, there was usually less than 10 per cent., and only once, in a case of severe acute gastro-enteritis,

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was it possible to identify between 10 and 15 per cent. of the fæcal nitrogen as ammonia.[1]

Disease.	*Fæcal Nitrogen per Day.*	*NH_3 Nitrogen.*	*NH_3 Nitrogen.*	*Remarks.*
	Gm.	Gm.	Per Cent.	
Granular kidney with cardiac failure	0·896	0·091	10·2	Diarrhœa.
	0·885	0·099	10·1	
	0·521	0·058	11·1	
	0·700	0·023	3·3	
	0·672	0·018	2·7	
Parenchymatous nephritis, with slight uræmic symptoms..	1·400	0·175	12·5	Diarrhœa.
Granular kidney	1·612	0·151	9·37	Diarrhœa.
	2·289	0·709	30·97	Watery stool.

4. Intestinal Putrefaction.

Biernacki demonstrated the presence of ethereal sulphates in the urine of six patients with acute nephritis (20). It was considerably in excess of the quantity found in the urine of healthy persons on a similar diet. From this may be inferred, though with some reservation, an increased amount of intestinal putrefaction. Biernacki holds that this is caused by cessation of the excretion of hydrochloric acid. The administration of this acid to his patients did, as a matter of fact, diminish the excretion of sulphuric acid. Biernacki's explanation, however, can hardly be the right one [von Noorden (30)]. It has been shown elsewhere that the absence of hydrochloric acid in nephritis is by no means invariable. The frequent increase of ethereal sulphates in the urine of renal patients has, however, been confirmed by Herter (3) in six out of eight cases. On the other hand, isolated investigations of L. Brieger (32) only showed traces of indican and phenol in the urine. My own results support, in certain cases, the positive results of Biernacki and Herter.

There is often a striking indican reaction and a large quantity of ethereal sulphuric acid in the urine of those not very infrequent cases where renal cirrhosis occurs in young people. From one point of view this may be regarded as a secondary phenomenon—*i.e.*, as a result of renal disease. On the other hand, it has been thought that the toxines formed in the intestines from the protein molecules, and their defective neutralization by the body, is a cause of the development of chronic renal disease [Blum (32)]. This is a suggestive theory, and demands further investigation. The ideas of Blum, however, hardly extend as yet beyond the region of hypothesis. In view of the scanty amount of positive material, a few figures which I have taken from the work of my assistant, M. Dapper, may be welcome.

[1] Immediately after evacuation the fæces were solidified in a freezing mixture, and only allowed to thaw again just before analysis.

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In every case a milk diet was adopted. In four out of six cases of acute nephritis the quantity of ethereal sulphate was less than 0·1 gramme (mean of three to four days); in two cases it rose to 0·14 and 0·15 gramme. In five cases of renal cirrhosis the amount was always more than 0·14 gramme, and usually between 0·18 and 0·24 gramme. No relation appeared to exist between the aromatic sulphates and the hydrochloric acid content of the stomach. Taking the diet into consideration, the quantity in acute nephritis is normal, and in renal cirrhosis unusually high.

IV.—INFLUENCE OF RENAL DISEASES ON THE URINE.

The most important manifestations of all renal disturbances are to be sought for in the condition of the urine. As the excretion of waste products becomes more difficult, kidney disease begins to seriously affect the other organs of the body and the general metabolism. Yet it would be a mistake to regard definite secretive conditions as characteristic of nephritis generally, or even of a special form of Bright's disease. Whatever form of renal disease is under consideration, great variations in the activity of the kidneys always coexist, and the excretion of individual substances is also so changeable that the disease, as a whole, presents no uniform picture. The researches of more recent years, carried out with improved methods, have fully confirmed the propositions which I advanced in my text-book on "The Pathology of Metabolism" (1893).

A.—THE TOTAL SECRETION OF NITROGEN.

It is laid down in almost all text-books that the amount of urea is diminished in all cases of diseased kidneys. Numerous isolated investigations confirm this view. Many authors go so far as to contend that diminution in the elimination of nitrogen is typical and invariable for each form of nephritis [Bond, Lifschitz (33)].

The excellent work of R. Fleischer (4) and the studies of J. Prior (26) —which, however, are not altogether convincing—appear to confirm this view. The first decisive results have been obtained from the experiments of C. von Noorden and A. Ritter (3), which have since been frequently confirmed.

It is obvious that the theory as to the elimination of nitrogen is only of value in cases where the amount of nitrogen in both diet and fæces has been determined, and where the investigations have not been limited to too short a period. The diet must, at all events, be fairly uniform in character, and its nitrogenous content easy to estimate. If the experiments do not fulfil these conditions they are of no value, except in isolated cases, such as those mentioned by Frerichs, Bartels, and S. Rosenstein in their text-books, where very marked deviations from normal conditions were present.

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To make these points quite clear, it may be stated that proteid disintegration follows the same rules in renal disease as in health. It is only in cases of uræmia that there is any question of heightened protein destruction leading to the production of toxines (*cf.* p. 435). If non-uræmic, renal patients be given a diet which in healthy individuals would establish nitrogenous equilibrium, either of the following results may occur:

1. The excretion of nitrogen through the kidneys will correspond to the quantity introduced, in spite of the disease. All the nitrogen excreted from the body is to be found in the urine if it has not been got rid of in the fæces. As a matter of fact, this normal condition may occur, especially in cases of renal cirrhosis.

2. The nitrogen excreted through the kidneys and in the fæces is markedly less than the quantity ingested. In these cases the nitrogen products of disintegration must either remain in the body or be got rid of by other organs, such as the lungs and skin. I must here emphasize the fact that the latter result does occur, but seldom to such an extent as to account for the nitrogen deficit which is frequently found. There is a third possibility: nitrogen retention may be avoided by the choice of a suitable dietary [von Noorden (34)].

3. More nitrogen is present in the urine than has been ingested. As the perviousness of the kidneys increases, the products of disintegration which have been retained pass rapidly away. The analogy between this fact and the physiological peculiarities of the nitrogen balance, where the patients are taking large quantities of water, is very obvious. It also reminds one of conditions that may obtain in heart cases.

Numerous investigations show that any one of these three possibilities may occur in cases of renal disease (35, 36). Indeed, all may be present in any one individual case, as also in the varying types of the disease.

The phenomena of *acute nephritis* are the clearest. In some of these cases days may elapse when only very small quantities or a few drops of urine are passed. The nitrogenous products of degeneration of these periods are, for the most part, stored up in the body, to be excreted later when the passage is once more free, together with newly-formed products of the same nature. Thus, in the first stage of the illness, less nitrogen is present in the urine than corresponds to the protein decomposition of the moment, while in the later stage—during recovery—there is a large percentage. In neither stage is the daily quantity of urine at all constant. On the contrary, in spite of an entirely uniform diet, great variations occur from day to day. As soon as free diuresis occurs, it frequently brings about the elimination of nitrogenous substances which hitherto have found no exit. It may happen, however, that this elimination may occur a little sooner, or one to two days later.

Without dwelling any longer on these obvious relations to the case just cited (p. 435), another example may be added (37). A child with scarlatinal nephritis at the commencement of the illness excreted in the urine 3·2, 6·5, and 4·5 grammes nitrogen. The quantity increased as the patient rapidly improved, and on two days amounted to 14·1 and 16·1

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grammes nitrogen. This occurred although the food intake was never more than 8 grammes nitrogen. Similar results are given in the works of Soetbeer (36) and von Noorden (38).

As already stated, such conditions are frequent in acute nephritis. On the other hand, acute cases occur, accompanied even by severe hæmorrhage, where the elimination of nitrogen is quite satisfactory throughout the whole course of the illness. I have often met with these conditions where nephritis occurred as a sequel to infectious disease. One patient with puerperal sepsis (37) developed hæmorrhagic nephritis on the fifth day. The amount of nourishment taken was extremely small (about ½ litre of milk and some sugar-water). On the first three days after the appearance of the nephritis she excreted in 1,000 to 1,150 c.c. of urine 12, 11, and 11·9 grammes nitrogen (independently of albumin)—that is to say, in spite of the nephritis, she maintained the increase in the nitrogen of the urine so characteristic of fever. Baginsky has met with a similar case, and other instances of the same kind are found in the works of Prior, Ascoli and Licci, Mohr and Dapper (35).

Such cases might, perhaps, be regarded as exceptional. Acute renal inflammation, if at all severe, occurring in persons who have previously been quite healthy, generally results in the retention of nitrogen during the initial stages. Unfortunately, it has not, as yet, been determined how long this condition may persist, nor is it known what quantity of urea and other nitrogenous substances may be retained in the more protracted cases. In those which have already been investigated, either an improvement of the excretory functions or death occurred within a short time—five to ten days.

The phenomena are more complicated in *chronic nephritis*. In the first place, since the thorough investigations carried out by Fleischer, it is well known that in chronic nephritis, as well as in acute Bright's disease, nitrogen may be retained to the amount of many grammes daily (4). This is true of the parenchymatous and interstitial forms of the disease, and also of amyloid degeneration of the kidneys. A little reflection will show the improbability of such a condition being a lasting one. Were it to persist, urea would soon be stored up in the body, not in grammes, but in kilogrammes. It might, perhaps, escape in small quantities through other organs, such as the skin, but it is quite certain that it could not be got rid of to any great extent (see below). On the other hand, C. Bartels states positively that, where the general nutrition and appetite are very good, and the diet rich, the excretion of urea in cases of chronic nephritis may reach a high and normal standard (40). The metabolism experiments of Fleischer point to the same conclusion, and so also do many instances quoted in more recent works.

The link which unites these apparently contradictory facts was pointed out by von Noorden and A. Ritter (3). It establishes, first of all, the fact that in cases of renal cirrhosis the capacity to eliminate nitrogen may be alternately either bad or good, or even very good. The period of retention is succeeded, either suddenly or gradually, by one in which nitrogen is again freely excreted. This nitrogen comprises that which results from the immediate albumin degeneration and that

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which has already been retained. Any one period may persist either for days or for weeks.

EXAMPLE 1.—With a food intake of 15·5 grammes nitrogen, a patient with renal cirrhosis excreted in the urine 20·1 grammes nitrogen (this was the period of free nitrogen elimination). Four days later the conditions were reversed, and on five subsequent days the total quantity retained amounted to 24·32 grammes nitrogen (41).

EXAMPLE 2.—A girl, aged twenty-two, suffering from parenchymatous nephritis and œdema, was found to have retained nothing out of 15 grammes nitrogen given in the food. She was in a state of nitrogenous equilibrium. Two months later 3·5 grammes nitrogen were retained each day. After six weeks the daily intake was 15 grammes nitrogen and the output 17·5 grammes nitrogen [von Noorden (4)]. The diet remained uniform throughout.

So far it has been impossible to determine the main differences between the phenomena of parenchymatous nephritis and of renal cirrhosis as regards their relation to the elimination of nitrogen.[1] It is, perhaps, safe to say that in cases of parenchymatous nephritis the elimination of nitrogen corresponds more closely to the amount of water passed and to the immediate severity of the disease than it does in cases of interstitial nephritis. This, however, is only a general statement, and is not necessarily true of any individual case.

Investigations have resulted in the demonstration of many interesting peculiarities.

Nitrogen was frequently retained in considerable quantities without any obviously uræmic symptoms being present, and even in cases where the general health was relatively good [Fleischer, P. Müller, von Noorden and Ritter, G. Ascoli, M. Kaufmann and Mohr, L. Mohr and C. Dapper]. The older observations of Christison, Babington, Rees, Frerichs (44), as well as others of more recent date, confirm this observation. In patients without any sign of uræmia much urea and other nitrogenous products of disintegration were present in the blood (see below). Neither the uræmic symptoms presented by the nervous system nor the other phenomena of renal cases make it possible to determine whether nitrogen is, or is not, being retained. As has already been remarked, this holds good to a greater extent in cases of renal cirrhosis than in cases of parenchymatous nephritis.

On the other hand, cases are recorded in which the elimination of nitrogen was excellent, and which yet developed uræmia [von Noorden and Ritter, Ascoli and Licci]. These, however, form rare exceptions. As a matter of fact, almost all observations regarding metabolism made when the patient is suffering from uræmia point to a more or less considerable retention of nitrogen. Where the reverse is true, an old remark of Bartels comes to mind that uræmic convulsions sometimes occur in cases where the œdema is already diminishing—at a time, that is, when

[1] Reliable determinations of the nitrogen balance for cases of granular kidney (42) in support of the theories here deduced are to be found in the works of Fleischer, P. Müller, Kornblum, Priór, Mann, von Noorden and Ritter, Köhler, H. Strauss, Rzetkowski, Butler and French, Kaufmann and Mohr, Mohr and Dapper, Soetbeer, L. Mohr, O. Rommel; for parenchymatous nephritis (43) in those of Prior, von Noorden and Ritter, von Noorden, Köhler, Ascoli and Licci, Dieballa and Illyés, M. Kaufmann and L. Mohr, L. Mohr and C. Dapper, L. Mohr; for amyloid degeneration in those of Fleischer, Kornblum, J. Mann, Soetbeer.

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nitrogenous extractives return from the tissues into the blood in large amounts, and so come into contact with the nervous system.

EXAMPLE.—The subcutaneous connective tissue was punctured in a patient, aged forty-five, who was in a transition stage between parenchymatous and interstitial nephritis. There was marked œdema, and the urine amounted to between 1,100 and 1,300 c.c. The diet had consisted for a long time of 2 litres of milk, 2 eggs, 200 to 250 grammes bread, plenty of butter, and 100 grammes of cane-sugar dissolved in liquids. The day following the puncture he passed 1,400 c.c. of urine, containing 9·7 grammes nitrogen, and 4 litres of œdematous fluid containing 3·8 grammes nitrogen (this was independent of the nitrogen contained in the proteins of the œdematous fluid). On this day the patient felt very well. On the second day diuresis increased to 2,200 c.c., containing 17 grammes nitrogen, and 6 litres of œdematous fluid with 6 grammes nitrogen were withdrawn. Twenty-eight hours after the puncture severe uræmic convulsions occurred, and did not subside until six hours later. The next day hardly any œdematous fluid escaped, and the urine (2,850 c.c.) contained 19·7 grammes nitrogen. The patient recovered perfectly at the time, but six months later died as the result of an acute recurrence of the œdema.

The elimination of nitrogen generally varies with the increase and subsidence of the œdema and the corresponding diuresis, hence the relation between the two is generally a simple one; but there are exceptions to this rule. As the œdema diminishes the nitrogen output is increased, but it does not follow that nitrogen will be retained as a result of increasing œdema. I have already mentioned two cases of this kind in my text-book on "The Pathology of Metabolism," p. 368. Similar observations are to be found in the works of my pupils, Kaufmann and Mohr (4) (Table I.), and Mohr and Dapper (27) (Table XII.), Claus, Plaut, and Reach (44A).

It has not as yet been definitely determined to what extent the retention of nitrogen may progress. Frequently 3 to 4 grammes nitrogen per day may be retained; sometimes there may be as much as 7 or 8 grammes, or even more. Unfortunately, most of the investigations extended over so short a period that it was not evident when retention gave place to free excretion.

I record here a trustworthy observation (in a case of parenchymatous nephritis) where 13 to 14 grammes nitrogen were ingested daily, and over a period of thirty days 146 grammes nitrogen were retained. In this instance the demand of the body for calories was barely met. During the thirty days there were five successive days when the amount of nitrogen excreted was rather in excess of that ingested. From the thirty-first to the thirty-sixth day 17·5 grammes of the surplus nitrogen was got rid of. At this point, unfortunately, the observations, for certain reasons, had to come to an end (analyses of food, urine, and fæces).

Where a change is effected from a diet poor to one rich in nitrogen it frequently happens that the elimination of nitrogen by nephritic patients increases more slowly than is the case with healthy persons [Prior, F. Hirschfeld (35)], and it is not unusual to find that variations in the nitrogenous content of the food do not clearly correspond to the nitrogenous content of the urine. The excretion of urea is especially apt to be very slow, whilst nitrogenous extractives are excreted more rapidly, and bear a much closer relation to the intake [H. Strauss, L. Mohr (45)].

Even when the excretory capacity of the diseased kidneys is, on the whole, good—*i.e.*, when on an average during eight to ten days or more

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the elimination of nitrogen corresponds to or exceeds the estimated amount of protein decomposition—the quantity of nitrogen in the urine often varies in the most striking manner. This variation greatly exceeds that of healthy people on a uniform diet. Von Noorden and Richter have already shown this, and many good examples are to be found in the papers of Kaufmann and Mohr, Mohr and Dapper.

Many attempts have been made to determine whether the form in which the proteid is given exerts any influence on the excretion of nitrogen (egg proteid, milk proteid, meat proteid, white and red meat). The differences are not important. The products of metabolism are better eliminated sometimes under one, sometimes under another form of diet [von Noorden and Ritter, M. Kaufmann and L. Mohr, von Noorden (46)].

The nitrogen excretion is to a large extent independent of the amount of liquid taken and of the corresponding diuresis. As a rule, the intake of water in cases of chronic interstitial nephritis may be limited to 1½ litres without affecting the excretion in the urine of solid substances, and especially of nitrogen. This is particularly true for granular kidney [von Noorden, L. Mohr and Dapper (47)], and justified me in reducing the quantity of fluid given to patients suffering from this disease. This is of importance in a disease so frequently accompanied both by hypertrophy and weakness of the heart [von Noorden (2)]. Clinical experience [L. Mohr and Dapper (27)] has not yet shown how far the same principle is applicable to parenchymatous nephritis. Theoretically, many objections have been raised [H. Strauss, E. von Koziczkowsky (48)] which have again been contradicted by other observations [L. Mohr (36), G. Kövesi and W. Roth-Schulz (48)], and by clinical experience. In the discussion opened by Hale White (British Medical Association, 1904), my theory that a moderate diminution of liquids is often indicated in cases of granular kidney was thoroughly upheld (48A). This position was also endorsed by P. F. Richter and F. Umber (48A).

All investigations go to show that the most striking characteristic of renal disease is the eccentric and unaccountable variations in the excretion of nitrogen. Factors which usually determine such excretion in a very definite way have much less influence than the variable excretory capacity of the kidneys themselves. The unaccountable and often sudden changes which this may undergo make it very difficult to arrive at any definite conclusion as to how far various methods of treatment (such as drugs, baths, change of diet, or of the amount of liquid given) improve or impair the excretive functions of the kidneys. It is quite certain that no trustworthy deductions can be made without most careful and conscientious inquiry, and unless many individual observations are carried out.

I must not conclude this section without reminding my readers that it is the theory of many physicians that nephritic patients should be given a diet poor in proteins [Senator, F. Hirschfeld, Albu (49), and others]. It is said that such a diet puts less strain on the diseased organs. No doubt this is true for acute nephritis and for the acute relapses of chronic nephritis, as I have emphasized elsewhere. For two years I

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have been of the opinion that in acute and dangerous cases no nitrogen should be given in the food. I have given nothing but sugar-water and fruit-juice for from three to eight days at a stretch (often 200 to 300 grammes of sugar daily). It was my impression that this form of treatment was very useful, and that uræmic symptoms were obviated, or if already present, were removed.

I cannot, however, admit that a long-continued diet of this sort is indicated by the investigations made into the nitrogenous condition of the patient in cases of chronic nephritis, and especially in cases of granular kidney. I myself, and various of my pupils, have communicated experiments and observations bearing on both the quantity and quality of protein forms of diet [von Noorden, Offer and Rosenqvist, Kaufmann and Mohr (50)]. As far as my clinical experience goes, any considerable and prolonged deficiency of protein in the diet affects injuriously both the state of nutrition and the general strength of patients suffering from Bright's disease, even though the excretion of albumin may be temporarily diminished. On the other hand, the interpolation of short periods (about eight to fourteen days) in which such a diet may be given can be thoroughly recommended in cases of parenchymatous and interstitial nephritis. Ernberg has recently recorded excellent results obtained by similar means (4A, 49A).

B.—VARIATIONS IN THE NORMAL NITROGENOUS CONSTITUENTS OF THE URINE.

Alterations in the relations of the nitrogenous constituents to one another may occur when the metamorphosis of nitrogenous derivatives follows an abnormal course, or owing to the fact that the diseased kidney excretes some substances with more difficulty than others. These considerations are of especial importance in nephritis, because uræmia has been ascribed to the retention of certain nitrogenous substances.

1. Urea and Amido-acids.

The relation of urea to other nitrogenous bodies in the urine of nephritic patients has been frequently determined since Gumlich made the first investigations into the subject (51). The methods adopted, however, are so different that the results cannot well be compared (52). According to the Mörner-Sjoqvist method, and all others involving the use of phospho-tungstic acid, it appears that, in all forms and all degrees of renal disease, either normal values are present—*i.e.*, the urea nitrogen constitutes 84 to 88 per cent. of the total nitrogen—or more frequently an even smaller percentage. This was often found to be the case during, or shortly after, an attack of uræmia. None the less, Ascoli is right in seeing no characteristic sign of uræmia in the relatively diminished amount of urea (53). The cause here is the increased excretion of ammonia, the extent of which, taken in conjunction with the smallness

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of the nitrogen total, must naturally lower the relative amount of urea. Quite independently, however, of the increase of ammonia (see below), the urea was frequently found to be diminished, especially where there was rapidly increasing dropsy. In these cases Gumlich only found 72 to 77 per cent. nitrogen present as urea. Three observations of mine confirm this. In one case of acute parenchymatous and interstitial nephritis, with an exclusive milk diet, and during rapid increase of the œdema, there appeared in the phospho-tungstic acid filtrate—

1. 72·8 to 74·3 per cent. of the total nitrogen (10·5 to 11·1 grammes nitrogen, exclusive of albumin nitrogen).

2. 74·3 per cent. of the total nitrogen (8·7 grammes nitrogen, exclusive of albumin nitrogen).

3. 75·5 to 73·8 per cent. of the total nitrogen (8·1 to 7·7 grammes nitrogen, exclusive of albumin nitrogen).

The ammonia varied between 0·6 and 0·8 gramme on the days of experiment, and thus was relatively, but not absolutely, increased.

The foregoing observations show that the renal conditions for the excretion of urea are frequently more unfavourable than those determining the excretion of other nitrogenous substances. Hence retention of nitrogen in nephritis always means, in the first place, retention of urea, whilst the retention of other nitrogenous substances cannot be so definitely deduced from the nitrogen deficit.

More recent investigations show that the quantity of urea was overestimated by the older methods. In the first place, Schöndorff, Pfaundler, Krüger and Schmid (54), have shown that, after precipitation by phospho-tungstic acid, the filtrates consist of amido-acids, oxy-protein acids, and perhaps other unknown bodies. Ordinarily, they constitute from 4 to 5 per cent. of the total nitrogen, and are present in rather larger quantities where a meat diet is given than with other forms of protein nourishment. This has been confirmed in my laboratory by A. Landau (55). In cases of renal disease this nitrogenous constituent of the urine has been found to be either normal in amount or somewhat above normal [Ascoli and de Grazia, von Jaksch, Halpern (52)]. The variations in the absolute and relative quantity of this fraction of the nitrogen, however, offer a striking difference from the conditions of health. Sometimes the higher figure coincides with the appearance of uræmic symptoms.

It seemed here that the variations might be taken to indicate certain qualitative alterations in the breaking down of the albumin, or even an explanation of the uræmic condition. But these theories do not stand the test of careful criticism (53). Here, as with other diseases, the question of amido-acids requires entirely fresh investigation, in so much as Embden has found amido-acetic acid, either combined or free, as a normal constituent of urine in measurable quantities (55A).

Moor has more recently stated that the filtrate, on precipitation with phospho-tungstic acid, contains other substances in addition to amido-acids and urea. A large part is said to consist of a compound, to which Moor has given the name of urein (56). The constitution and occurrence of this substance is not yet sufficiently determined [Gies (56)].

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2. Ammonia.

Gumlich (51) states that on a diet poor in protein (milk, white bread) the subjects of renal disease excrete small quantities of ammonia, and on a varied dietary normal quantities of ammonia. This was also found to be the case in four patients with interstitial nephritis who were under Hallervorden's observation (57). Other estimations give similar results (58). It certainly happens that the relative proportion of ammonia often exceeds the normal average (3 to 5 per cent. of the total nitrogen). The cause of this, however, lies in the diminution of the total nitrogen, such as the urea, rather than in the increase of the ammonia, which is obviously one of the easily excreted substances [von Noorden (38)].

This is equally true of all forms of nephritis. It is only in cases of uræmia that the ammonia tends to increase absolutely as well as relatively. Still, it was, as a rule, less than 1 gramme daily. I found the highest amount in a patient suffering from renal cirrhosis with acute uræmia—1·80 grammes NH_3 nitrogen to 9 grammes total nitrogen [von Noorden (59)]. I do not, however, agree with Senator (60) when, on the ground of the slight increase of the amount of ammonia, he ascribes uræmia to that form of auto-intoxication which is typically associated with abnormal acidity (acidosis). The output of ammonia in uræmia is far too small. Further, it must be remembered that most uræmic patients take hardly any nourishment, or vomit what they take immediately. It is much more probable that in these cases the acidity and the increase of ammonia are the result of inanition.

3. Purin Bodies.

The behaviour of alloxur bodies in renal disease is very important. The purin bases formed in the body are, together with uric acid, closely related chemically to caffeine, theobromin, and theocin, all of them substances which act powerfully on the heart and bloodvessels. As these organs are seriously affected in cases of nephritis, one is justified in asking whether the retention of purin bodies, and especially of their bases, in the blood may not contribute to the circulatory disturbances which accompany nephritis.

Uric acid is especially difficult to excrete. The older literature states that it may be diminished, or even altogether absent, from the urine of renal patients (61). This is certainly a mistake, as Frerichs has already remarked (62). The methods employed were inadequate. The results obtained with improved methods by van Ackeren and Stadthagen (63, 64) showed that a normal proportion of uric acid was present in every form of Bright's disease. These statements were confirmed shortly afterwards by Weintraud and Kam (65, 66). Where the average proportion is normal, the uric acid is subject to very slight, and the urea to much greater, variations. From this I conclude that the diseased kidneys excrete uric acid more easily than urea (67).

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This was the position when Kolisch and Fodor directed attention to the relation between uric acid and alloxur bases (68, 69). According to Kolisch, nephritic patients excreted a relatively large proportion of purin nitrogen (40 to 50 per cent. instead of about 15 to 25 per cent.) in the form of bases. This recalls an old observation by Baginsky (70), who found a slight increase of xanthin in a case of acute nephritis. Kolisch deduced from these facts a far-reaching hypothesis regarding the formation of uric acid by the healthy kidney and the impairment of this function in nephritis. My former assistant, Zülzer (71), has proved conclusively that the facts do not justify this new theory. Kolisch used a method which gave too high figures for the alloxur nitrogen. Hence only the uric acid estimates are reliable in most works relating to the determination of the varying proportions of alloxur substances to uric acid (72). With the adoption of more reliable methods the relation of uric acid to the alloxur bases was found, as a rule, to be perfectly normal (73). Daily and individual variations were no greater than in healthy persons. The investigations of Kaufmann and Mohr (73) are of especial value, because they prescribed a diet which would really enable them to determine the amount of endogenous purin nitrogen in the urine. The following average figures were obtained :

Disease.	*Total Purin Nitrogen.*	*Uric Acid Nitrogen.*	*Total Nitrogen.*
	Gm.	Gm.	Gm.
Acute nephritis :			
Case I.	0·129	0·106	18·4
,, II.	0·145	0·130	13·6
,, III.	0·156	—	9·6
Interstitial nephritis :			
Case I.	0·184	0·151	17·0
,, II.	0·169	—	14·5
,, III.	0·203	0·172	13·8
,, IV.	0·109	0·094	15·5
Parenchymatous nephritis :			
Case I.	0·179	0·145	13·1

These results show that, on a purin-free diet, nephritic patients excrete on an average 80·4 per cent. of the purin nitrogen as uric acid, and the remainder as bases. This corresponds with the figures obtained by Burian and Schur, Kaufmann and Mohr, Walker Hall, from healthy persons on a similar régime. Benjamin gives a somewhat lower figure for bases (average of seven observations = 0·021 gramme of alloxur bases ; in healthy persons he found 0·025 to 0·035 gramme). He says nothing, however, about the nature of the diet (73). When it is remembered that most of these patients are ordered a diet poor in purin (small quantities of meat and few extractive substances), the figures frequently given—among them those of Kolisch—appear relatively high. On the other hand, the functional impairment of the kidneys might naturally result in the excretion of a very small quantity, and uric acid would be retained in the blood (see below). Where this small amount is not the result of

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a monotonous purin-free diet, it indicates serious deterioration of the filtrative capacity.

As a rule, the inflamed kidneys react to a diet rich in purin almost as favourably as in health. Examples of this are to be found in the works cited under reference (75). Similar investigations carried out by my assistant, Schliep, point to the same conclusion. These experiments were made on healthy persons, and on the subjects of nephritis and gout. Only in gout was the quantity of uric acid considerably reduced.

	Average Uric Acid (Gm.).
CASE I. (SCHLIEP).—Acute Nephritis:	
Five days; purin-free diet	0·387
Two days; purin-free diet + 400 grammes beef	1·012 0·739
Two days; purin-free diet	0·495 0·540
CASE II. (SCHLIEP.—Chronic parenchymatous nephritis:	
Five days; purin-free diet	0·543
Three days; purin-free diet + 400 grammes beef	0·697 0·810 0·790
Five days; purin-free diet	0·616 0·573 0·400 0·383 0·586

None the less, retention takes place in cases of renal disease. Figures which only fall a few centigrammes below the usual average may appear normal, and yet a small daily deficit in the amount excreted may result in a considerable accumulation of uric acid in the blood.

Generally speaking, however, the proposition I have laid down in my text-book on "The Pathology of Metabolism" holds good—that the diseased kidney is relatively pervious to uric acid; any considerable retention of uric acid usually goes along with a still more considerable retention of urea.

4. Creatinin.

Since Hofmann found that the amount of creatinin was greatly diminished in some very severe cases of renal disease, it has been thought that it belonged to those substances which the diseased kidney excretes with great difficulty (76). Hence the fear of its accumulation in the blood formed one cogent reason for forbidding meat extracts and a meat diet generally. Later investigations have not wholly confirmed this opinion. Certain cases are, indeed, mentioned where, along with a considerable lessening of the general diuresis, the excretion of creatinin also diminished (77). As a rule, however, the figures for creatinin cannot be regarded as low if, as is natural, we take into account both the intake of creatinin and the total output of nitrogen. The analyses of Tedeschi, D. G. Zanoni, Troitzki, L. Mohr (78), suggest that creatinin is more easily excreted by the diseased kidney than most other nitrogenous substances, especially urea. This is most patent in an observation by Mohr (36). His patient was suffering from acute nephritis, and was on an exclusive milk diet (1,500 c.c. of milk). She excreted on an average 11 grammes nitrogen and 0·56 gramme creatinin. A second investigation gave 9·4

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grammes nitrogen and 0·65 gramme creatinin. When 25 grammes of Liebig's meat extract and 3 grammes of urea were given in addition to the milk, 11 grammes nitrogen and 2·2 grammes creatinin were excreted. Both experiments showed a normal reaction to the introduction of creatinin, whilst the first experiment evidenced a retention of urea. In another case the kidneys did not excrete the introduced creatinin and urea to any extent. This proves how impossible it is to estimate the capacity of the kidneys as regards the total excretion of nitrogen, and how difficult it is to generalize from individual observations on this point.

Zanoni's work tends to show that the excretion of creatinin is altered more in chronic interstitial nephritis than in the acuter forms of the disease. This question requires further investigation.

The conditions which determine the excretion of creatinin are all the more interesting because of the former tendency to attribute uræmia to the retention of this substance (creatinæmia, Jaccoud). This had its origin in the discovery of creatin in the blood of uræmic patients, and received further support when Landois (97, 80) found that creatinin injected into the cerebral cortex of animals produced convulsions and coma. This poisoning, however, only followed after the injection of creatinin, not after that of creatin [Bouchard, Feltz and Ritter (81)]. Traces only of the former are found in the tissues; otherwise it is formed by the kidneys themselves at the moment of excretion. No specific toxic effect is now attributed to the retention of creatin.

5. Hippuric Acid.

It is stated by Jaarsveld and Stocvis, Stocvis and von d. Velde (82), that in cases of parenchymatous nephritis the synthesis of benzoic acid and glycocoll in the kidneys is only imperfectly accomplished, and that only a small proportion of ingested benzoic acid is found as hippuric acid in the urine of these patients. Von Schröder and Schmiedeberg do not consider these theories as established, since Stocvis used a method which was not a reliable one.

On the other hand, Kronecker (84) observed defective formation of hippuric acid in nephritis; but, unlike Stocvis, he found it more defective in cases of interstitial than in parenchymatous nephritis. Recent experiments with better methods, and where the nature of the diet was very carefully considered, are not favourable to Stocvis's (85) views, but go to show that spontaneous excretion of hippuric acid is not more difficult than that of any other substance. The addition of benzoic acid to the diet yielded varying results, as in the case of healthy persons. The question has lost much of its interest since it has been recognised as probable that other organs besides the kidneys are able to synthesize hippuric acid. This is not the case with carnivora. At the same time, the matter deserves further inquiry. It is now evident that glycocoll may be considered as a normal constituent of the urine (whether free or combined is not yet fully determined). This fact was not known to earlier investigators (55A).

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C.—THE EXCRETION OF WATER AND OF SALTS; MOLECULAR CONCENTRATION AND ELECTRICAL CONDUCTIVITY.

The excretion of nitrogenous substances in nephritis, both collectively and as individual constituents, shows marked deviations from the normal condition. The quantity varies both above and below the average. As to the several constituents, although some of them seem more easily excreted than others, yet it is quite impossible, excluding those cases which are either extremely slight or extremely grave, to make any rule as to what will happen in this respect in any one particular stage or form of the disease. The same holds good of inorganic substances. It is only as regards the excretion of water that any definite rules can be enunciated, and these correspond more to the general clinical condition than to the excretive and filtrative capacity of the kidneys.

1. Excretion of Water.

The excretion of water shows the most striking variations. It may be arrested until complete anuria is set up, or the urine may amount to litres daily. It is best to consider only the simple facts of clinical observation.

In *acute nephritis* the quantity of urine generally diminishes considerably at the onset of the disease, and usually at the same time when œdema is developed. This is most obvious in scarlatinal nephritis, in which the primary seat of the lesion is glomerular. In these cases it is only the incapacity of the kidneys that is responsible for the rapid diminution of diuresis. There is neither molecular nor hydrostatic pressure of the blood. Moreover, the oliguria is found to be independent of the supply of fluid. In the first severe stages of the disease this supply increases the œdema, but not the diuresis, or only to a very insignificant extent. It is, therefore, quite useless to give the patient large quantities of fluid in order to "wash out" the kidneys. Such a measure only irritates unnecessarily an organ which is already impaired [von Noorden (38)]. The spontaneous increase of diuresis is the first and surest sign of convalescence, or of transition into a chronic condition. Œdematous fluid is excreted, and the kidneys at the same time begin again to react to the amount of liquid given.

EXAMPLE.—A girl of fourteen, with acute scarlatinal nephritis, was taking daily 1,500 c.c. of milk. To this was added 1 litre of weak tea on the third and seventh days of the observation.

Day.	*Quantity of Urine.*	*Extras.*
	C.c.	
1	550	—
2	320	—
3	350	1 litre tea.
4	300	—
5	820	—
6	1460	—
7	2310	1 litre tea.
8	1670	—

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Another instructive example is given by Kövesi and Roth-Schulz (85A).

Oliguria and polyuria do not alternate with any very definite regularity. In the oliguric period single days occur when the quantity of urine increases, and, on the other hand, when the flow of urine is free, there are days when oliguria is present.

In other cases of *acute nephritis* it may happen that, during the whole course of the illness, the amount of urine is only slightly diminished, and reacts much more obviously to variations in the quantity of liquid given. This is most frequently the case in the hæmorrhagic nephritis which may form a sequel to acute infectious disease (pneumonia, erysipelas, typhus, sepsis, etc.).

When the excretion of water and the reaction to the intake of water are lessened in cases of acute nephritis, it generally happens that the output of solid substances is also lowered (we are not here considering albumin). In chronic interstitial nephritis, on the other hand, it is frequently found that this parallel does not hold good. Thus, as long as oliguria persists in acute nephritis the valency figure (depression of the freezing-point in a sample of the total quantity of urine passed during twenty-four hours) is considerably below normal, whilst the molecular concentration of any one sample may remain within the normal limits. The defective reaction to the amount of fluid taken is all the more striking when it is a question of the physical analysis of the urine. The freezing-point of the urine—that is, its molecular concentration—varies hardly at all, whereas in healthy people this is not the case. Two examples given by G. Kövesi and W. Roth-Schulz (86) illustrate this :

	Average Hourly Diuresis.		*Freezing-point Lowered.*	
	Spontaneous.	After 1,800 c.c. Salvator Water during Three Hours.	Spontaneous.	After 1,800 c.c. Salvator Water during Three Hours.
	C.c.	C.c.		
Normal	52	723	1·33°–2·17°	0·09°–0·75°
Acute nephritis ..	91	103	0·60°–0·75°	0·53°–0·87°

I consider that clinical experience justifies these authors in affirming that the defective adjustment of the kidneys to a varying water-supply is an important clinical symptom. It is more characteristic of, and it is found more invariably in, cases of acute nephritis than either oliguria, hyposthenuria, and oligovaluria. (For the definition of these terms, see pp. 381 and 458.)

The conditions in *parenchymatous nephritis* are very different, and may vary in individual cases. The variations are more periodical, and do not come to an end in a few days, as in acute nephritis. Each individual case generally maintains its peculiarities—as regards the excretion of water—for a longer time. Cases occur where there is only slight diuresis. If the amount of water taken is not limited intentionally, they

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are, almost without exception, accompanied by œdema. When larger quantities of water are given [Marischler (27); *Verdünnungsversuch*, by Kövesi and Roth-Schulz (86)], the increase of diuresis and the decrease of molecular concentration are subnormal. Where this is the case the excretion of free substances is naturally neither favoured nor increased. In such circumstances the condition of the patient is aggravated by an unlimited supply of water, the superfluous fluid only increasing the œdema.

Cases where, with a free supply of fluid, diuresis remains normal, or is even slightly increased, are much more rare, as also are those where dropsy supervenes, notwithstanding good diuresis, amply sufficient for a healthy person. Although it is not difficult to increase diuresis, even up to a normal amount, by giving plenty of water, the dropsy persists and increases. This shows that the kidneys have by no means lost their capacity to excrete water.

On the other hand, cases in which there is no œdema, and where the variations in the diuresis correspond to those of the intake of fluid, are sometimes met with. Clinically, these must not be regarded as cases of simple parenchymatous nephritis, but as being in a state of transition to interstitial nephritis.

In parenchymatous nephritis the output of water is usually closely allied to the elimination of solid substances. If one compares different cases this fact is not so obvious. In individual cases, however, the excretion of urinary substances rises and falls with the diuresis (always supposing the diet to be the same), although they are not always contemporaneous.

The molecular concentration of the urine remains, on the whole, fairly constant. The freezing-point of the urine does not rise with the taking of water, or, if so, only to a slight degree, and very slowly (*Verdünnungsversuch*). Above all, it does not fall proportionately to the introduction of excretable substances—*e.g.*, sodium chloride (*Verdichtungsversuch*). [Examples are given by Koranyi, Kövesi and Roth, Strauss, Nagelschmidt, Loeper (89)]. Whilst the molecular concentration and the amount of the urine keep below the normal average the total output of the extractives of metabolism remains insufficient, oligonuria taking place [Lindemann, Senator, H. Strauss (90), and others]. Numerous exceptions, however, may occur with regard to diuresis, as well as with regard to the molecular concentration of the urine (91, 92). Thus, a very complex picture is presented; the conditions at one moment approximate to those which are present in the severe initial stages of acute nephritis, and at another to those of renal cirrhosis.

When the amount of fluid taken is left to their own discretion, and the heart keeps strong, patients with granular kidney excrete a copious and dilute urine ("compensated renal cirrhosis"). They quickly react to increase and diminution in the fluid intake by corresponding variations in the diuresis, just as does a person in health. Every practitioner has had personal experience of such cases, and many examples are to be found in treatises on the metabolism of renal patients [especially in those by L. Mohr and C. Dapper (27)]. The freezing-point of the urine is

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found to rise proportionately in the so-called "dilution experiments" (*Verdünnungversuch*) (89), although not always so quickly and uniformly as in health. Exceptions occur, especially in those stages of the disease where the heart has already been impaired. Further, it is to be remembered that the course of granular kidney is frequently interrupted by exacerbations in which the clinical picture resembles that of acute nephritis.

No one will deny that patients with typical granular kidneys, compensated by hypertrophy of the heart, pass a dilute urine (glomerular function), and that this may be further diluted by the taking of water. Strauss, however, is of opinion that it is impossible for cases of renal cirrhosis to excrete a sufficiently concentrated urine (93). In order to cleanse the blood of extractives, they require a most copious supply of water. The enormous diuresis and increased thirst of these patients are in some measure compensatory phenomena, for only thus is oligouria avoided. I do not understand how Strauss arrives at these conclusions. In the many publications on cryoscopy (including those of Strauss himself) examples are to be found where cases of renal cirrhosis excrete a urine of normal or even higher molecular concentration than that of healthy persons. This fact becomes very obvious if the freezing-point of each individual sample of urine is tested, and not merely the mixed urine of twenty-four hours. By this means anyone will become convinced that in any case of polyuric renal cirrhosis he may investigate, some one or other sample of urine will be found to be entirely normal, both as regards its specific gravity and molecular concentration. If hyposthenuria is present in the majority of the samples and in the daily total, it must be attributed mainly to increased diuresis. I might assert that the polyuria is not primary, but only a result of the polydipsia. How to explain this is another question. Strauss's view cannot be made to accord with any theory as to the secretion of urine, least of all with the usual theory that an extremely dilute sodium chloride solution is excreted by the glomeruli, and that a portion of the water is reabsorbed in the tubules. According to this view, which Strauss also accepts, cases of renal cirrhosis must, if his theory is correct, be the first to suffer as regards the excretion of sodium chloride. This is contrary to the facts, and my own experience, that patients may do excellently on a limited supply of water, not merely for weeks and months, but for years, is entirely opposed to his view (38). My pupils, Mohr and Dapper (27), have also shown that, within certain limits, the most important constituents of the urine can be got rid of with only a limited water-supply—just as well, in fact, as when one imposes no restrictions on the polydipsia and polyuria of the patient. Conversely, Kövesi and Roth-Schulz (85A) state that, "in cases of compensated interstitial nephritis, with increased capacity for the secretion of water, the attempt to increase the elimination of nitrogenous products, to further molecular diuresis, and to combat the tendency to retention in the blood by a copious supply of water, has not been successful." Naturally, this only holds good within limits. Patients with interstitial nephritis, just like persons in health, cannot reduce the quantity below a certain limit without impairing the excretion of the products of metabolism. This limit, as shown by Mohr

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and Dapper (27), is about 1,250 c.c. of fluid daily (independently of water contained in solid food).

I think the facts are as follows: Every patient with chronic nephritis suffers from abnormal thirst, and if left to himself will drink copiously. This thirst is caused by peculiar chemical conditions in the blood, but whether it is set up by the usual and well-known products of metabolism (urea, salts, etc.), either directly or only indirectly by raising the osmotic pressure,[1] or whether other substances not as yet chemically identified are responsible for it reflexly, must for the present remain undecided. The excretion of urine in oliguric renal patients (type: very acute and chronic parenchymatous nephritis) is not proportional to the intake, either because the capacity of the kidneys to excrete water is impaired equally with or more than its other functions, or—and there is a good deal to be said for this view—because the tissues themselves attract and retain water. The polyuric patient (type: granular kidney, with good compensation, and the later stages of acute and also of chronic parenchymatous nephritis) maintains hydrostatic equilibrium because his kidneys, with the aid of a hypertrophied heart, retain, or have regained, the capacity to excrete water freely. It is not, however, certain that he will be able to get rid entirely of the solid substances which should pass out in the urine. In spite of polyuria, this function, which is to a large extent independent of the quantity of urine excreted, may be severely impaired, or, to put it in a more modern form, polyuria may be associated with a high degree of oligomoluria. [Examples are given by Fleischer, von Noorden and Ritter, Koranyi, Lindemann, Strauss, Claude and Balthazard (94)]. (In Bradford's well-known experiments the secretion of a large amount of dilute urine and a watery condition of the blood were associated with marked reduction of kidney tissue—a condition similar to that which obtains in granular kidney. To quote Beddard, "it is the effort of the reduced kidney substance to excrete the maximal amount of material with a minimal expenditure of energy.") The urine of the polyuric renal patient is poor in molecules not because his kidneys cannot excrete a urine with a high molecular concentration, but because he drinks copiously. If one puts reasonable restrictions on the fluid intake (for other reasons a wise and useful measure), the amount of urine diminishes. The specific gravity and the molecular concentration increase as in health, and the total output of solids is scarcely altered. Spriggs (Oliver Sharpey Lectures, *Lancet*, 1906, vol. i.) suggests that practically the effect of large quantities of fluid upon the vascular system is not so great as theoretical considerations would lead one to expect.

This is true of granular kidney with good compensation. Practically, however, the phenomena are much more varied. Renal cirrhosis is the *Proteus* amongst diseases, not only as regards the general clinical symptoms, but also as regards the excretive capacity of the kidneys. No one case wholly resembles any other, and in each good and bad periods alternate (see section on Œdema).

[1] This opinion is supported by von Koranyi and his pupils Kövesi and Roth-Schulz. However probable it may seem, it must be remembered that we also find a great increase of thirst in hydræmic renal patients, and that the molecular concentration of their blood is subnormal.

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2. Cryoscopy and Electrical Conductivity.

Cryoscopic investigation of the urine of renal patients demands consideration. The hopes aroused by Dreser's and Koranyi's admirable work have vanished within a few years (95, 89).

The urine contains organic and inorganic molecules in true solution. As a result, its freezing-point is lower than that of water. The difference may be expressed by the sign Δ. In the mixed urine of twenty-four hours the lowering of the freezing-point was found in healthy persons to vary between $-0{\cdot}87°$ and $-2{\cdot}43°$. Examination of individual samples showed even greater variations. In consequence of the uniform relations which exist between the number of dissolved molecules in a solution and the freezing-point, the latter affords a convenient test for its molecular concentration. If this is increased, the condition is termed hypersthenuria, and if lowered hyposthenuria. If the amount of the lowering of the freezing-point is multiplied by the quantity of the urine, a value for the total molecular output results. This product (Δ × quantity of urine) is termed "valency value," as suggested by Strauss (89). In healthy people it varies considerably—from about 1,000 to 3,500. Pathological deviations, above or below, are denoted by the terms "polyvaluria" and "oligovaluria" respectively. It is convenient for many purposes to reckon the valency value in terms of its sodium chloride equivalent [Koranyi (89)]. The quotient $\frac{\text{Valency value}}{61{\cdot}3}$ enables one to determine approximately how many grammes of sodium chloride must be contained in the urine in order to produce the given freezing-point. If this estimate has been arrived at, and the true sodium chloride content of the urine determined, it is possible by subtraction (sodium chloride equivalent − sodium chloride content) to arrive at the sum-total of the other urinary substances in solution.[1]

Quantity of urine	=1500 c.c.
Δ	=1·40°.
Valency	=2100.
NaCl equivalent	=2100 ÷ 61·3 = 34·2 grammes.
NaCl in urine	=10·8.
NaCl equivalent of the other dissolved constituents	=34·2 − 10·8 = 23·4 grammes.

In normal urine the determination of the freezing-point is hardly more instructive than the specific gravity. The latter also depends upon the degree of concentration, and this fact and the quantity of urine may be very important factors in determining the total excretion of

[1] The doubtful element in estimating the NaCl equivalents lies in the fact that all urines have the same degree of disassociation of a 1 per cent. solution of sodium chloride [A. Steyrer (97)] for all their inorganic molecules. Urine which has been diluted to one-tenth of its usual density promises more accurate values as regards the determination of the freezing-point and the estimation of its products because, with this degree of dilution, the disassociation of all salts has reached a definite constant [Zangemeister (98)]. The formula would then read $\frac{\Delta \times \text{total quantity of urine} \times 10}{0{\cdot}613}$. Very concentrated urine must be diluted from fifteen to twenty times, and the multiplication figure altered correspondingly. The figures 0·613 in the divisor indicate the lowering of the freezing-point in a 1 per cent. NaCl solution.

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solid substances (Häser's coefficient). If, however, the urine contains albumin the position is altered. The specific gravity will be greatly affected by the large and heavy albumin molecules, but the freezing-point hardly at all — *e.g.*, 2 per cent. of urea lowers the freezing-point of water by 0·616°, 2 per cent. of albumin by only 0·0037°. Hence cryoscopy is a better test than the specific gravity of the output of extractives (salts and organic products of metabolism) in urine containing albumin. But cryoscopy has also its dark side, and is a fruitful source of error. This is due to the disassociation which takes place in watery solutions of salts. The greater the dilution, the greater the disassociation of salts. The disassociated NaCl molecule acts, not as one, but as two units; the disassociated Na_2SO_4 molecule not as one, but as three units, on the osmotic pressure (freezing-point). In dilute urine the freezing-point will be relatively lower than in concentrated urine, and though the amounts of solid substances may be absolutely equal (urea, NaCl, and other salts, etc.), the product of the depression of the freezing-point × the quantity of urine (the important valency value) will be considerably higher in dilute than in concentrated urine. Although Koeppe has already pointed out these sources of error, practical cryoscopy has not taken them into consideration (99). They account for many apparent contradictions. Zangemeister has recently recommended that each specimen of urine should be diluted until the disassociation degree has reached a definite and approximately constant maximum before the cryoscopic determination is made. For this, dilution of from ten to fifteen times the volume of distilled water is sufficient (98).

The following example shows the effect of this method: For undiluted urine (1,216 c.c.) a valency value of 1,012 was found, and after dilution one of 1,189 was found (a difference of 15 per cent. !). Zangemeister's suggestion is well worth considering. At all events, he excludes the most important source of error in cryoscopic determinations.

Whilst cryoscopy permits an estimation of the content of the urine as regards the extractives of metabolism, uninfluenced by the addition of albumin and albuminous substances, it is possible by measuring the electrical resistance (Kohlrausch's apparatus) to find that of the inorganic salts. Only these, or possibly their disassociated ions, conduct the electric current in a solution. Since Turner and Bugarsky (100) introduced this method many determinations of electrical conductive capacity have been carried out (101). Dawson Turner (379) measures the electric resistance of the blood, as well as that of the urine. From this he obtains " the hæmo-renal salt index "—namely :

$$\frac{\text{The electrical resistance of the blood.}}{\text{The electrical resistance of the urine.}}$$

Normally, this = 2·08. This index indicates the salts, acids, and bases, and is practically unaffected by the presence of albumin, sugar, and other non-electrolytes. Cryoscopy measures the total molecular concentration. In conjunction with cryoscopy, this method affords a very satisfactory insight into the composition of urine. By means of the

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former we are able to estimate the total amount of solids excreted, and by the latter the amount of inorganic and, after subtraction, that of organic matter [A. Steyrer (97)]. These are important factors in estimating the total excretive capacity of the kidneys. The result is much more instructive than that afforded by the separation of the products of excretion into chloride and other constituents, which is only useful where the problem is a very limited one. It must be remembered that the expression of the valency value in terms of its NaCl equivalent, as recommended and practised by Koranyi, Lindemann and Strauss, is, from the physical-chemical point of view, a very doubtful proceeding (see above).

The following statements as to the three physical methods of investigation may now be made: All solid constituents of the urine, including proteins, may be estimated by determining the specific gravity. After precipitation of the albuminates the specific gravity gives the same results as cryoscopy.

Cryoscopy determines the presence of all molecules which are contained in true solution (exclusive of albumin) (102). By determining the electrical resistance, the free ions, in the first place, and also the inorganic salts are measured. So far the new methods of cryoscopy and electrical resistance show that the values which they determine are, in the urine of nephritis, frequently less than normal; that they are subject to considerable variations; and that the administration of water —sodium chloride urea—(possibly albumin) to renal patients produces in one a corresponding degree of concentration of the urine, in another an insufficient reaction or none at all. Hence they only afford an expression in physical terms of a well-known chemical fact.

Recent writers consider that too high a value should not be attached to the figures obtained by cryoscopic methods (103). Still, these methods have a certain signification and justification. They afford, without the employment of chemical tests, a rapid—if superficial—insight into the activity of the kidneys—superficial, that is, as compared with the results obtained by chemical analysis. By determining the amount of the most important constituents of the urine the latter yields information which the physical methods only indicated—namely, that renal disease produces alterations in the selective capacity of the kidneys in relation to the excretion of the constituents of the blood. It is only for the analyst that inorganic salts, on the one hand, and organic extractives, on the other hand, are sharply separated groups. The diseased kidney behaves quite differently in regard to the individual members of each group. Besides, chemical analysis permits a comparison between the intake and the output, and it is only when both the quality and quantity of the intake have been ascertained that it is possible to estimate the positive activity of the kidneys. A knowledge of the chemistry of the food opens the way to a better understanding of the much more simple chemistry of the excretions.

When the first doubt arose as to the value of cryoscopy for estimating bilateral kidney disease, an attempt was made to make use of it, at all events, to compare the functional activity of the right and left kidneys

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respectively. As a means of deciding which kidney was diseased, and in reference to operative interference, the question was an important one (104). Apart from quite obvious differences—*e.g.*, right kidney polyuria, hypersthenuria, and polyuria; left kidney oliguria, hyposthenuria, oligomoluria—the applicability of the method stood or fell with the question whether both kidneys always produced an approximately similar secretion, both as regards quantity and quality, or whether considerable differences are present even in health. The authors, who assumed that similarity of function in both kidneys was normal, would have been saved from much confusion on this point if they had studied more carefully the researches made in the middle of last century which laid the foundation for the study of this subject [Hermann, Ludwig, and others]. A new statement on the point has now become necessary in order to combat these recent assertions, and to show that, even in health, the right and left kidneys may, during identical periods, differ considerably from each other, both in relation to the quality and the quantity of the urine passed [Biedl and Krauss, Bardier and Frenkel, Israel, Goebell, Kapsammer (105)]. The future will show whether comparative cryoscopy of the urines secreted by the left and right kidneys respectively possesses any value for diagnosis.

3. Salts.

The excretion of salts in renal disease is subject to great variations. In this it resembles the excretion of nitrogenous substances. Retention may occur, followed by compensatory copious excretion. Older communications seem to show that the retention periods and the excretive variations are not so important as in the case of urea [Frerichs, Bartels, von Noorden (106)]. This can no longer be entirely maintained—at any rate, as regards chlorides. The individual salts must be considered separately, because the chlorides are excreted by the glomeruli and the phosphates by the tubules.

(*a*) *Chlorides.*

In my text-book on "The Pathology of Metabolism" I was able to make the following deductions from my records regarding the metabolism of renal patients: "The NaCl output often corresponds exactly to the intake. Where there is retention of urea, the output of NaCl is decreased, but not to so great an extent as that of the urea. Occasionally the NaCl elimination succeeded a period in which both it and urea were retained, but the nitrogen output did not vary correspondingly. I never saw the converse occur. It is probable, therefore, that the kidneys were more permeable for the NaCl than for urea."

More recent investigations into the excretion of sodium chloride show that it varies more than at first appeared. Marked differences in the NaCl elimination have been observed, and an attempt has been made to classify them—*i.e.*, to bring certain forms of NaCl excretion into causal connection with certain forms of nephritis. This appears to me at

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present a somewhat hazardous proceeding, for against each observation adduced to support a particular formula others can be cited which entirely contradict it.

Frequently—one may say generally—the excretion of NaCl does not materially differ from that of healthy persons—that is to say, it corresponds in some measure to the intake. Such cases with a normal NaCl equilibrium are to be found in the works of Bohne, Hofmann, Lindemann, Marischler, Loeper, Mohr, Soetbeer, Halpern (107). They may occur in any form of nephritis. As far as it is possible to judge from the data given, a good excretion of NaCl occurred chiefly at those periods when the diuresis and the output of nitrogenous extractives were altogether or almost satisfactory, such as the later stages of acute nephritis, periods of free diuresis in parenchymatous nephritis, and compensated interstitial nephritis. It was, however, frequently observed, even where the excretion of chlorides was satisfactory, that the output corresponded less promptly to the intake than in normal individuals. When the amount of chloride in the diet is moderately increased, a healthy person will regain chloride equilibrium in from twenty-four to twenty-eight hours; a nephritic patient would often not achieve this for some days.

In other cases more considerable deviations from the normal condition may occur.

1. Even with a uniform diet the excretion of chlorides often varies more from day to day than is the case in health. This is also true of most of the other urinary constituents, and cannot be regarded as an indication of grave disturbance. Examples of this are given by L. Mohr (36), von Koziczkowsky (108), Halpern (107).

2. Sometimes the urinary chlorides are not merely equal to, but are far in excess of the NaCl intake—*e.g.*, in some cases cited by Hofmann, Marischler, Widal, and Javal (109), Halpern, Umber (48A). Such excretion indicates that sodium chloride, which had previously been accumulating in the blood, was being excreted as a result of an improvement in the renal functions. It is astonishing how large these amounts may be—*e.g.*, in sixteen days a patient of Halpern's (subchronic nephritis) lost, together with a disappearance of the œdema, 208·6 grammes NaCl—more than he had ingested (daily intake about 5·6 grammes NaCl). An output to this extent is certainly unusual. It must here be mentioned that by simply prescribing a diet poor in chlorides (2 to 6 grammes NaCl daily) similar results may be often attained. Both healthy persons and nephritic patients in whom retention of chlorides has not occurred would, with this small NaCl intake, regain their chloride equilibrium within a few days. According to Achard this equilibrium may be attained by adults on a daily intake of 29 NaCl (40).

Chloride equilibriums relating to this second group were found in cases recovering from acute and subacute nephritis, in chronic parenchymatous nephritis and its transition stages to renal cirrhosis, but less often in fully developed granular atrophy. These were patients who had either had severe œdema, which disappeared as the chlorides were got rid of, or who were predisposed to œdema.

We must not generalize, however. This warning is nowhere more

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necessary than in that branch of the pathology of metabolism which deals with nephritis. For this reason I use the words "eccentric, unforeseeable," as expressing the true characteristics of the metabolic equilibrium in renal disease. Further confirmations of this view may be cited. Cases have been known where not a diminution, but an increase, in the NaCl intake has led to a lessening of the amount of chlorides in the body—*i.e.*, the presence of a larger quantity of sodium chloride stimulated the capacity of the kidneys for its excretion, so that a copious outflow of the substance ensued [L. Mohr (111)]. Perhaps it is not superfluous to remark that this fact was observed in a case which gave persistent signs of a tendency to *petite urémie*, and which some weeks later succumbed to uræmia [L. Mohr (36)]. Claude relates a similar instance (112).

3. There are also cases of nephritis which undergo periods of considerable chloride retention, and the urine of which only contains small quantities of NaCl. This point has been but recently brought forward. Bohne (107) was the first to make a definite communication on the point, and his work has since been confirmed by many other investigators [Marischler, Ch. Achard and M. Loeper, H. Claude and Mauté, A. Hofmann, F. Widal and A. Javal, von Koziczkowski, H. Strauss, A. Steyrer, M. Halpern, L. Mohr, G. Kövesi and W. Roth-Schulz, etc. (113)]. These numerous observations may be generalized as follows:

(*a*) In unilateral renal disease the urine of the affected kidney was frequently poorer in sodium chloride than that of the healthy kidney (114).

(*b*) In certain cases of bilateral renal disease an abnormally small quantity of sodium chloride was excreted, and its addition to the diet did not lead to any, or only a very insufficient, increase in the output. It even happened that this treatment impaired the capacity of the kidneys to excrete this substance still further. The NaCl retention amounted, according to the intake and the severity of the disease, sometimes to a few decigrammes and sometimes to several grammes daily. Thus the tissues accumulated a large amount of sodium chloride. Sometimes large quantities of sodium chloride were excreted through the intestines, which thus did the work which should have been done by the kidneys [Javal (115)]. This, however, only happened when severe diarrhœa occurred, as it sometimes does in the final stages of nephritis. Considerable quantities also were vomited [Javal and Widal, Bing (116)]. Such vicarious excretion, however, is seldom present, and, as a rule, the gravest disturbance of the renal functions in this respect does not result in any increase of chloride in the fæces [Halpern (107)].

The retention of chloride in renal disease, even when considerable, is not pathognomonic. At first it was described as present in acute fevers. Lately Achard, Loeper, Laubry, and F. Müller (117) have found it under the most varying circumstances—*e.g.*, in lobar pneumonia, typhoid, rheumatic fever, gall-stones, tuberculosis of the lungs, carcinoma of the stomach, etc. According to Marie (118), it may also occur in healthy persons, although only if an excess is contained in the diet.

(*c*) In many cases chloride retention only persisted as long as there was a moderate or large amount of sodium chloride in the food. A

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diminution of this (from about 2 to 5 grammes daily) led to an increase in the amount excreted, and in a short time to a very considerable output. Such examples are cited by Widal, Halpern, Claus, Plaut, and Reach (44A), and others. It must, however, be borne in mind that the exact converse of this has also been recorded, and that attempts to stimulate the renal capacity to excrete sodium chloride by adding NaCl to the diet resulted in imperviousness of the kidneys to this substance.

(*d*) As already pointed out, the NaCl excretion runs somewhat parallel to that of nitrogen [von Noorden (21), Soetbeer (36), and others]. Cases, however, have been described in which the renal capacity to excrete sodium chloride was very much less than the capacity to excrete any other urinary substance, including water. As regards sulphates, phosphates, and purin bodies, this is not a matter for surprise, as they are got rid of in other places—*e.g.*, in the tubules. What is more remarkable is that the behaviour of urea [Widal and Javal (119), Strauss (19)] and water [Mohr (36)] may be quite different from that of NaCl, although all are excreted via the glomeruli [Koranyi, Loewi (120)]. Thus, the capacity of the diseased kidney to deal with the various urinary substances cannot be predicted.

If one reviews the cases in which considerable retention of sodium chloride occurs, those of acute nephritis at its worst and the severe forms of chronic parenchymatous nephritis are chiefly concerned. In granular kidney this condition only obtains during acute inflammatory exacerbations, or when the cardiac compensation is failing. These are all conditions which either coexist with œdema or exhibit a very marked tendency towards œdema. From a clinical point of view they must be described as extremely grave and dangerous. Only prolonged clinical experience can show whether the appearance of the retention of chloride has a far-reaching significance as regards prognosis, or whether it is only indicative of a temporary condition. In the absence of this factor, it is impossible to regard the classifications of Widal and Javal (119), Claude and Mauté (113), and Strauss (121) as final.

The sodium chloride question has become one of especial importance because of its close association with the presence of œdema in nephritic patients. Certain relationships are obvious. Pure water does not enter the tissues as such ; it always contains organic and inorganic substances in solution. Hence, with an increase of œdema, there must be a retention of urinary substances, and when the œdema subsides a corresponding outflow of such bodies. This has long been known, and has rendered necessary the exercise of great caution in estimating the metabolic equilibrium in œdematous patients [von Noorden (34)]. Sodium chloride is the urinary substance *par excellence*, which seems to play an especially important part in relation to œdema. The relation of NaCl elimination to œdema may take different forms, as follows :

1. The retention of water may be primary. This may be due to incapacity of the kidneys, or to weakness of the circulation, or to the abnormal perviousness of the vessels, or to the attraction of water by the tissues. The water thus retained requires sodium chloride in order to balance the osmotic pressure of the blood. Hence, as long as the œdema

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is increasing the output of sodium chloride by the kidneys is diminished [Marischler (27)].

2. The sodium chloride deposit in the tissues may be the primary cause, and the water follows in accordance with osmotic laws.

Opinions differ as to the cause of the primary NaCl retention in the tissues. Achard (122), Loeper, and Laubry seek for the cause in a chemical alteration of the tissues themselves. They recall the fact that the same thing has been observed in many other diseases which have not been accompanied by impairment of the kidneys. At the same time, Achard admits that the diminution in the capacity of the kidneys to eliminate NaCl is a new and important factor in the enrichment of the tissues by chlorides, and increases the attraction capacity of the tissues for water.

Bohne, Widal, Kraus, Strauss, Claude and Moog, Halpern (123), Kövesi and Roth-Schulz, and others, attribute retention of sodium chloride to functional incapacity of the kidneys. Widal and Strauss lay especial insistence on the fact that, where renal œdema is developed, the elimination of chlorides by the kidneys is always diminished. The NaCl which cannot find an exit from the body attracts the water.

Widal and Strauss consider the imperviousness of the kidneys to sodium chloride as the key to the whole problem with regard to œdema. I do not think that this extreme position is justified. Other factors must be taken into account (see section on Œdema). None the less, it is certain that sodium chloride bears a relation to one of these factors, and it is much to the credit of these investigators that they have laid the utmost stress upon this fact.

Javal and Widal describe a convincing and much-quoted case (124). An addition of chlorides to the diet resulted in œdema, a diminution of chlorides produced free diuresis. This experiment was repeated many times in succession, and always with the same results. Similar examples (production of œdema on the addition of chlorides, and their insufficient excretion) are given by Halpern, Kövesi and Roth-Schulz, Claus, Plaut, and Reach. There is no doubt that the retention of chlorides in these cases occasions the retention of water. But this is not always the case. The observation of Claus, Plaut, and Reach may be cited in this connection. In a prolonged investigation extending over fifty-five days (acute nephritis passing into the chronic parenchymatous form) periods occurred in which the œdema increased at times when the excretion of sodium chloride was also increasing (44A).

There is no uniform correspondence between the enrichment of the tissues by water and chlorides on the one hand, and the excretion of water and chlorides on the other hand. In a litre of blood-serum obtained from a nephritic patient 5 to 6 grammes of NaCl were found, and in a litre of œdematous fluid 6 to 7·5 grammes [Strauss, Halpern (123)]. It must be admitted that in many cases during the rise and fall of the œdema the theoretical proportions required are approximately present (examples are given by Halpern, Kövesi and Roth-Schulz; individual periods by Claus, Plaut, and Reach). Yet the same authors record, even in different stages of the same case, marked deviations from these relations —*i.e.*, at one time an excess of chloride is retained, and at another an

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excess of water. A patient of Halpern, for instance, lost 2,250 grammes in weight in ten days (this was mostly water, as the intake of calories was sufficient), and 34·3 grammes NaCl (the sodium chloride contained in this amounted to 1·08 per cent.). At another time the same case retained only 5·3 NaCl and 3,000 grammes of water, which corresponded to a 0·17 per cent. solution. Such conditions as these are practically never present in the tissue fluids. In other cases the differences between the theory and the facts were still more striking. Considerable NaCl retention occurred without an obvious or measurable degree of œdema, and again there was a copious secretion of NaCl long after the œdema had disappeared—*e.g.*, in a case quoted by A. Hofmann (107)].

Marie has advanced a hypothesis in explanation of these phenomena. A certain quantity of salts can be taken up and chemically fixed by the tissues themselves (*chlorure fixé*). This deposit is not indicated by any corresponding alteration in weight. The fixation occurs in the preliminary stages of œdema, and persists even after diuresis is set up. It is only after the water has been got rid of from the tissues that the condition comes to an end. Hence it happens that cases occur in which retention of chlorides is not accompanied by retention of water, and also cases where chlorides are excreted, and yet diuresis is not present. It is only after saturation of the tissues that the chlorides accumulate in the tissue fluids. Here they attract water, in order to maintain osmotic equilibrium, and set up œdema (*chlorure libre*). The chloride and water equilibrium is approximately parallel to the retention and output of the "free chloride." Such cases have, as a matter of fact, been described. The proportion of water and chlorides they presented almost corresponded to the degree of concentration actually present in œdema (three observations by Halpern). There is much to be said for Marie's hypothesis. It has recently been shown that the tissues enrich themselves with matters that have been retained much more quickly and to a much greater extent than do the circulating fluids, and this is true equally for an excess of water [Engels (124)] as for retention of solid substances [R. Rosemann (125)].

This section must not be concluded without calling to mind the hypotheses which assume that chloride retention plays a part in uræmia. Lindemann supposes that there is hypertonia of the fluids caused by retention of sodium chloride (90), Bohne that the chlorides exercise a specific toxic action. Neither view is established, since many cases of extensive sodium chloride retention without uræmia have been observed, and conversely of uræmia without NaCl retention (see Uræmia).

(*b*) *Sulphates.*

The variations in the sulphates run somewhat parallel to those of the nitrogen (126). The observations of Biernacki and Soetbeer (127) confirm this, as well as the case investigated by Claus, Plaut, Reach. The relation N : S corresponded to the structure of the albumin molecules. The same results appear in the majority of Licci's cases (128).

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Yet these analyses of urine show that sulphates were excreted more easily than nitrogen. Conversely, a retention of sulphates, as compared with nitrogenous substances, is described—*e.g.*, in a case of amyloid kidney cited by Fleischer, and another by Soetbeer. The variations of sulphates and of nitrogen are often in quite opposite directions, as Stocvis records (129), and as I myself have found in acute and chronic parenchymatous nephritis even with a uniform diet [von Noorden (130)]. On the whole, the sulphates and the aromatic sulphates may be regarded as easily excreted substances. But observations which extend over longer periods of time are necessary, for very rapid variations occur with these, as with other urinary constituents, and have to be taken into account. Neither the scanty and incomplete observations of von Koziczkowski (108) nor the statistics of Licci (116) convince me that there is an invariable antagonism between the output of chlorides and of sulphates.

(*c*) *Phosphates.*

Fleischer found in several cases of nephritis of varying types that the excretion of phosphoric acid diminished when the excretion of urea was lowered, and also—and this is a point of great interest—when the excretion of urea was normal. The so-called relative phosphoric acid value (100 P_2O_5 : N) was always remarkably low. From this Fleischer concluded that the diseased kidney excreted phosphates with great difficulty, the result being that they accumulated in the tissues. The assumption is most probably correct, as the fæcal P_2O_5 was not increased. Although more recent literature contains some examples which confirm this view—*e.g.*, Rzetkowski (3), individual cases of Marischler (2), Mohr (36), Licci, Roth-Schulz and Kövesi (128)—still, Fleischer's actual communications, as he himself suspected, are not conclusive, either for all cases or for every stage of the disease. It must be regarded as almost accidental that Fleischer did not meet with a case in which the amount of phosphoric acid did not exhibit the same relation to the nitrogen as obtained in the food taken. Such cases are now known to exist in large numbers [von Noorden and Ritter, Prior, Kornblum, van Ackeren, Mohr, Soetbeer, Marischler, Mohr and Dapper, Licci (131)]. It is to-day possible to state that the P_2O_5 rises and falls in nephritis just as do all other urinary constituents, and that frequently, though not invariably, the capacity of the kidneys to eliminate phosphoric acid undergoes very considerable deterioration. An antagonistic relation to NaCl, as recorded by Koziczkowski (108) in individual cases of renal insufficiency, and as indicated also by Rzetkowski (3), is certainly not the rule (*cf.* the cases of Mohr and Licci, Claus, Plaut, Reach). A retention of phosphates and sulphates as severe and as prolonged as that of chlorides has never been observed.

(*d*) *Potassium.*

I can only find records of the excretion of potash in renal disease in Soetbeer's observations (35), who gives an account of it in a case of granular kidney and in one of acute nephritis. In both of the cases the

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output corresponded to the intake, and that at a time when uræmic symptoms were present. Seeing that for a long time uræmic symptoms were attributed to potash-poisoning, this discovery is remarkable. The nature of the diet, which consisted principally of milk, fully explains the fact that, in both cases, the excretion of potash considerably exceeded that of the Na_2O (the average in the first case with a plentiful diet being 3·56 grammes K to 1·65 grammes Na; in the second case, with a meagre diet, 0·84 gramme K to 0·31 gramme Na), for milk is poor in Na and rich in potash.

(*e*) *Calcium.*

There are only a few records of the excretion of calcium [Marischler (27), Soetbeer (35)]. The figures given by the latter are strikingly low (in the first case the average was 0·046 gramme, in the second 0·066 gramme). This suggests retention, as the diet (milk) was rich in calcium. Marischler's experience points to the same results (parenchymatous nephritis). The analyses of the food and fæces showed that small quantities of calcium were always retained in the body. This subject demands further investigation.

D.—ALBUMINURIA.

1. Tissue Albumin or Food Albumin.

When it was discovered that the urine of nephritic patients contained albumin, it was impossible to identify the type of albumin present. The general view identified it with the proteids of the blood, and this opinion has persisted, although it was very soon pointed out that there were indications which suggested the direct transmission of the proteids of the food into the urine [Brown-Séquard, Teissier, Lauder Brunton and Power (132), etc.]. It was only when a biochemical test was applied that the question was satisfactorily settled. When the blood-serum or the urine of nephritic patients is injected into rabbits, the blood-serum of the animal contains precipitins for the albumin of human urine or blood-serum [Mertens, Zülzer, Dieudonné, Ascoli, Aschoff (133)]. Although these investigations must be regarded with a certain amount of caution [Umber, Rostocki (134)], still, the proof of the identity of the proteids in the blood with those of the urine from nephritic patients may be considered as established. Erben has recently demonstrated in the same way the biochemical identity of the serum globulin with that of the globulin of the urine (135).

Other researches, moreover, showed that food-albumins, as well as tissue albumins, pass into the urine of nephritic patients (136). The biochemical reaction in the urine of egg-albumin, milk-albumin (not casein), and of beef has been established. At the same time only very small quantities of food-albumin appear in the urine, since by far the

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larger proportion is so changed by gastric digestion that its characteristic biochemical reaction is lost.

In nephritis the albumins are mainly excreted by the glomeruli, as was demonstrated long ago by microscopic and microchemical investigations. Jul-Schmid demonstrated the same fact in another way when he showed that the elimination of albumin by the glomeruli runs parallel with that of the other substances which they excrete (136A). At the same time, under certain circumstances—*e.g.*, in experimental vinylamin-poisoning—other portions of the kidney share in the elimination of proteids [F. Müller (117)].

Where acute inflammation occurs, resulting in inflammatory œdematous infiltration of the whole organ, all parts of the kidney share in the excretion of proteids from the vessels and in their transmission into the urine.

2. Albumin and Globulin.

As a rule, serum albumin (synonym "serin") and serum globulin are contained in the urine of nephritic patients, together with traces of the food-albumins. Under certain circumstances nucleo-albumins may also be found. In hæmorrhagic nephritis, of course, all the proteid bodies of the blood are present in the urine. Cases occur where either one or other of the proteins is predominant, either permanently or temporarily. This is termed serinuria [Hoffmann, Boyd, Strauss (137)] or globinuria [Werner, Maguire, Chauffard and Gourand (138)], or nucleo-albuminuria [Pichler and Vogt, Madsen, Strauss (139)]. All these are extremely rare as yet; they cannot be satisfactorily explained. The records extant must not be regarded as absolutely reliable. The methods employed for the differentiation and identification of the proteids are not, for the most part, sufficiently satisfactory.

Hoffmann gives the term "albumin quotient" to the relation $\frac{\text{Albumin}}{\text{Globulin}}$. Many investigations, partly clinical, partly experimental, have been carried out in order to determine its relation to renal disease (140). The hope that the albumin quotient would show definite and differentiating values in the varying forms of renal disease has only been partially fulfilled. The urine of nephritic patients usually contains more serum albumin than globulin, so that the albumin quotient amounts to 1·5 to 2·3. Variations above and below these limits may take place, not only in different cases, but also in the same case on different days. But, on the whole, Czatary's view, which has been arrived at after very careful investigation, seems to confirm the theory that in cases of granular kidney there is a marked excess of serin. This author is of opinion that the high blood-pressure and the very rapid circulation in the kidneys is unfavourable to the excretion of globulin. Cloetta, on the other hand, thinks the condition is caused by the state of the filtrating membrane (140). The less dense the kidney tissue, the more easily can globulin find an exit (acute and chronic parenchymatous nephritis). Where the disease results

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in tissue induration there is a predominance of serum albumin. Dreser and Lommel have also expressed similar views (140).

An attempt has been made to discover what relations exist between the association of both serin and globulin in the blood on the one hand, and in the urine on the other. So far, however, no definite conclusion has been arrived at, either as to the relative serin and globulin content of the blood [Czatary, Noel-Paton, Cloetta, Erben (140)], or as to its molecular concentration. The cause, therefore, of the variations of the proteid quotient in nephritis is still an open question. In the meantime, its solution is of greater interest from the point of view of practice and diagnosis than of theory, since it has been established that the globulin content frequently exceeds, or nearly approaches, that of the serum albumin in lardaceous disease of the kidneys. Senator (141) was the first to demonstrate this fact, which has since been frequently confirmed [Reale, Erben, Joachim (142)], although some investigators quote instances which contradict it [Petri, Noel-Paton (140)]. The albumin and globulin present in the urine have the same nitrogenous content as that of the blood [Marchetti (143)].

3. Nucleo-albumin and Euglobulin.

Most of the researches hitherto made into the relations of serin and globulin are open to the objection that they have not definitely removed the other proteids precipitated in the undiluted urine by acetic acid, with the result that these bodies were added to the precipitated globulin. They were first found in the urine by Müller (144), and soon after by Moritz (145) in exudations, and were termed "globulin." Von Noorden (146) at first identified them as mucin, an error which became apparent when Obermeyer (147) demonstrated the presence of phosphorus in the acetic acid precipitate. Since then this body has been termed nucleo-albumin. It is now generally known that this proteid body precipitated by acetic acid is frequent in cases of fever, in jaundice, heart disease, and in parenchymatous nephritis. It is also often present in healthy persons who have undergone physical exertion. It appears to be an integral part of so-called physiological albuminuria (148), a view held by Senator, von Leube, von Noorden, and others. The theory took a new direction when Mörner (148) showed that in the urine of such persons a large part, perhaps the whole, of the acetic acid precipitate consisted of pure proteid combined with substances already present (taurocholalic acid, but chiefly chondroitin sulphuric acid). In the meantime Stähelin and Joachim (150) emphasized again the globulin-like nature of these proteids, and Matsumoto, Rostoski, Calvo, and Oswald (151), as a result of fractional precipitation, arrived at the conclusion that the acetic acid precipitate consisted of a mixture of euglobulin and fibrinogen. Mörner, however, held fast to his position, and for good reasons (152). In any case, more recent investigations [Matsumoto and Oswald on the one hand, and Mörner on the other hand] clearly show that this body exists sometimes independently and sometimes in con-

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junction with ordinary albuminuria; that it can certainly be precipitated by acetic acid, but that it is not to be identified with nucleo-albumin. If, as appears to be the case, Mörner's view is the correct one, this proteid body has no particular pathological significance; it is ordinary proteid which has only become capable of precipitation by acetic acid as the result of special combination with other substances. If it is identical with euglobulin, the case is different. As A. Oswald has shown (153), it diffuses with more difficulty than albumin. If it is found more frequently and in larger quantities than albumin in certain cases of so-called physiological albuminuria, yet, in view of its different diffusibility, it cannot be caused by a "greater perviousness of the renal filter." On the contrary, according to Oswald, euglobinuria indicates "irritability of the kidneys." The whole question needs further consideration.

It does not seem to me, however, that the question of nucleo-albuminuria can be altogether put on one side. True nucleo-albumin frequently accompanies albuminuria in fever cases, and is present in variable, but often quite considerable, quantities in most forms of acute nephritis. Its source lies, undoubtedly, in the cell elements of the blood and kidneys. From the point of view of pathological metabolism these simple combinations are not of any great interest, with the exception of one discovered by Jolles (154), who found "nucleohiston" (with a phosphorus content of 3·14 per cent.) in the urine of a patient suffering from pseudo-leuchæmia.

The copious acetic acid precipitates which are often met with in cases of constitutional albuminuria in young persons are still more remarkable. Attention was first drawn to these as a distinctive element in the clinical condition by Pavy (155), under the name of "cyclic albuminuria," and at the same time and quite independently by von Noorden (146). It is probable that the condition subsequently described as "orthostatic albuminuria" and "albuminuria of puberty" belongs, for the most part, to the same category of cases. They must not, however, be confused with the albuminuria of true nephritis, which, as we know, may also be intermittent. For the nosological classification of this constitutional albuminuria I would refer the reader to the works of Pavy, von Noorden, Klemperer, Oswald, Heubner, and von Leube (156). In spite of von Leube's excellent communications, these cases of cyclic juvenile albuminuria are not altogether clear (136). I have already pointed out that in this form of albuminuria a "peculiar and globulin-like body is present in quantities which exceed those of the serum albumin" [von Noorden (157)]. I based this statement on its strong reaction to acetic acid. In the many typical cases which in the meantime I was able to observe, this reaction produced a massive, dense precipitate, insoluble in excess of acid, and often only slightly increased by the addition of ferrocyanide of potash. The same body has also been observed in similar cases by Flensburg, Pavy, Pommerehne, Pribram, and Oswald (158). It seems to be identical with the protein found by Schreiber, Pichler and Vogt, and others, in cases of compression of the thorax (159). I am in entire agreement with Pribram, who regards this body as possessing particular sig-

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nificance in diagnosis in cases of juvenile constitutional albuminuria (158). I might add that it is also significant in prognosis, for it is my opinion, based on an observation of cases which has extended over many years, that where this body is present in large quantities true nephritis does not exist.

Further investigation is needed in order to determine whether this body is a nucleo-albumin or a special type of globulin. My investigations, which, however, were not carried out on the pure substance, do not lead me to identify it with the above-mentioned acetic acid precipitate first described by Müller (144) and Moritz (145) as present in the urine of patients with fever, jaundice, heart disease, etc.

The nature of the process which leads to the albuminuria of adolescence (cyclic albuminuria, Pavy) is also, as yet, not clear. In addition to the theories which assume "increased perviousness of the kidneys" (Leube) and "irritability of the kidneys" [H. Senator (157A)], there is another hypothesis to consider, one which takes into account the chemical alteration of the blood proteins: the kidneys are pervious to pathological proteids, and transmit them into the urine. I brought forward this theory in my first work on the subject, and called the condition diabetes albuminosus [von Noorden (146)]. Langstein (158A) has recently drawn attention to it again. As protein bodies precipitated by acetic acid seldom occur singly, one has to assume that some of the ordinary proteins of the plasma are precipitated with them. In the same way white of egg injection never passes into the urine alone, but is always accompanied by true blood proteins.

So far it has not been observed that any form of metabolic disturbance accompanies, or is the cause of, the albuminuria of adolescence [Langstein (158B)].

It is possible that the copious excretion of oxalates is in some way organically associated with the appearance of the proteid body precipitated by acetic acid, for in typical cases it is never absent [von Noorden (146)]. Langstein, who had previously expressed this opinion (158A), has recently declared that no significance is to be attached to the presence of oxaluria (158B), since high oxalate values are also found in the urine of other children. I do not, however, consider the question as settled.

Some authors attribute albuminuria to a low blood-pressure, especially in those cases where it disappears when the patient is lying down and recurs when he assumes the erect posture [Edel, Loeb, Pelnar (158C)]. The upright position involves a copious supply of blood to the muscles and an increased intra-abdominal blood-pressure, with the result that the circulation of blood in the kidneys becomes slower. In certain individuals this brings about from time to time a perviousness of the epithelium of the kidneys to proteins. This view, however, cannot be maintained without assuming a peculiar "predisposition" on the part of the patient, for there are many weakly and anæmic persons, with a permanently low blood-pressure, who never excrete the slightest trace of proteid material.

The following examples by Pelnar are of cases in which the blood-

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pressure underwent considerable diminution when the patients were in the upright position :

Lying Down.	*Standing.*	*After Lying Down again.*
105 millimetres Hg pressure	65 millimetres	—
120 „ „	75 „	130 millimetres.

Wright and Ross (*Lancet*, vol. ii., 1905, p. 1165) measured the salt contents of the urine and blood-serum by determining the dilution necessary for these fluids to completely dissolve a definite quantum of red blood-corpuscles, and concluded that the renal function is entirely unimpaired in cases of "physiological albuminuria." They consider that in this condition there is a transudation of lymph into intact urinary tubules. They observed a diminution in the coagulability of the blood in several cases of physiological albuminuria, and point out that active exercise, nervous disturbances, and assumption of the erect posture—the usual accompaniments of this manifestation—all produce an increased hydrostatic pressure in the renal capillaries. The increased pressure plus the diminished coagulability of the blood would dispose to transudation of lymph. By treating their cases with calcium lactate they were able to effect a rapid disappearance of the albuminuria.

4. Albumoses.

The urine of nephritic patients does not usually contain any hydrated proteid. This fact is stated by the older investigators [Maixner, Pacanowski (160)]. Discoveries of a positive nature, however [Gregoriantz, Senator, Gérard (161)], lead one to doubt the methods employed. I have frequently ascertained that albumoses may be formed after excretion from the proteids present in the urine of patients the subjects of kidney disease [Ulrich (162)]. This transformation is effected either by the pepsin which is always found in the urine in this disease [Mya and Belfanti (163)], or by micro-organisms. Investigations regarding the presence of albumoses in urine containing proteids are of no value unless made when the urine is perfectly fresh. This question has recently been considered anew by Jolowicz (164), a pupil of Rostocki, who found in fourteen cases that hydrated protein was never present.[1] So far it is only in the urine of fever cases that a positive trustworthy result has been obtained [Krehl and Matthes, Haak (165)], and this is dependent on the nature of the fever rather than on any irritation of the kidneys.

[1] The negative results obtained by Jolowicz are certainly not conclusive. Hofmeister found that albumoses were contained in the precipitate. Vang's method makes it almost impossile to separate off small quantities from the precipitate. Jolowicz certainly made control determinations, but it is obvious that he added too much hydrated proteid to the control.

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5. Reaction of Albuminuria on Metabolism.

Albuminuria is so insignificant in some forms of slight and of severe renal disease that the loss of protein is quite negligible. On the other hand, it is questionable to what extent the considerable loss of protein which occurs in chronic parenchymatous nephritis, in certain cases of interstitial nephritis, and in lardaceous disease, may damage the tissues generally, especially the protoplasm. It is well known how many theories have been advanced in regard to this subject, and how popular a theme it has become amongst pathologists.

Clinical experience shows that patients may excrete considerable quantities of protein through the kidneys for many years without any evident effect upon the system, providing that they are given a plentiful diet. Researches into the metabolism of renal disease point to the same conclusion. I will quote one out of the many examples available: A patient of von Noorden and Ritter (166), suffering from parenchymatous nephritis, lost 227 grammes in the urine in twenty-four days (9·4 grammes daily). In spite of this loss, nitrogenous equilibrium was maintained. Her diet consisted of about 26 calories per kilogramme of body-weight (no œdema). The food contained about 97 grammes protein, of which 87 grammes were absorbed. The protein disintegration was similar to that of a healthy person, who would absorb daily 77·6 instead of 87 grammes. This excess of 9·4 grammes compensated the body for what was lost by the daily outflow of albumin in the urine.

This is an actual proof that a severe degree of albuminuria does not lead to any impoverishment of the body in protein if the diet is rich in nitrogen. It is uncertain what would happen were the food poor in nitrogen.

Another patient of mine in a transition stage between parenchymatous nephritis and contracted kidney, with a tendency to diarrhœa, took 3 litres of milk daily for three weeks. The nitrogen intake amounted to 15·2 grammes, the output on an average to 1·9 grammes nitrogen in the fæces, 1·3 grammes nitrogen as urinary albumin, and 12·3 grammes nitrogen in the other nitrogenous substances of the urine. The excretions certainly varied very much from day to day, but, on the whole, the nitrogenous equilibrium was maintained. During the next three weeks 1 litre of milk was omitted, and in its place 100 grammes of carbohydrate and 25 grammes of butter were given, together with 900 c.c. of water. In view of the diminution of the protein intake, the diet was thus altered to ensure the same intake of calories and water. The nitrogen given amounted to 10 grammes daily. There is no doubt that a person in health would, under such conditions, have maintained the nitrogenous equilibrium (32 calories) per kilogramme during absolute rest in bed! This patient excreted 2·05 grammes nitrogen in the fæces, 1·15 grammes nitrogen in the form of urinary albumin, and 8·3 grammes nitrogen in the other nitrogenous substances of the urine. The loss to the body was, therefore, 1·5 grammes nitrogen daily (31·5 grammes nitrogen in three weeks). This case throws an unfavourable light on the prevailing custom

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of prescribing a diet poor in protein for all forms of nephritis. The large amount of nitrogen present in the fæces, and the considerable loss of albumin in the urine, may bring about a condition in which the nitrogenous equilibrium can no longer be maintained. It is true that the emaciation of the body might be successfully counteracted by increasing the intake of carbohydrates and fats, but this would involve a certain addition of fat to the body, which is not desirable in cases of nephritis [von Noorden (167)]. For clinical reasons which I have stated elsewhere I am of the opinion that the protein intake should be reduced to the lowest possible limit in acute nephritis, but that in all chronic forms of albuminuria the daily intake should not fall below from about 80 to 90 grammes, otherwise the patients become weaker and frailer than can be accounted for by the nature and severity of the disease [von Noorden (36)].

Ernberg, who has made a most careful clinical and experimental study on the value of a low protein diet in cases of renal disease, comes to the same conclusion (4A). He recommends for chronic cases the frequent interpolation of short periods (four to five days), when a diet very poor in proteids should be given, in order to facilitate the elimination of accumulated nitrogenous extractives. This recommendation ought to be generally adopted.

It is a matter for considerable doubt whether, as was formerly thought, hydræmia and hypalbuminosis of the plasma are caused by a loss of protein, for they occur in acute and subchronic nephritis when there is certainly no extensive loss.

6. Influence of Diet on Albuminuria.

An investigation of this subject is only of importance if the thesis can be maintained that the degree of albuminuria affords a test of the severity of the disease. This supposition is only partially true. No one would now regard the granular atrophy of one patient as more serious than that of another because the former excreted a large and the latter a small quantity of albumin. The same is true for other forms of Bright's disease. The only point to be discussed is whether in one and the same case the rise and fall in the excretion of albumin is to be regarded as unfavourable or favourable respectively. In acute nephritis it must be admitted that they are to be so regarded. Small daily variations in the amount (about 15 to 25 per cent.) are, it is true, of no value in prognosis, but greater alterations, when accompanied by inverse changes in the amount of urine, are of considerable importance in estimating the severity of the disease. A large amount of albumin and little urine must be regarded as a bad symptom, whilst little albumin and increased urine is a good sign. In granular kidney the position is reversed. It is quite useless to compare the amount of albumin present in the urine at the moment with that excreted weeks or months before. A patient is misled who is congratulated on the fact that, whereas he formerly lost a large amount of albumin, he is now excreting only a small

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quantity. The most that can be said is that it is doubtful whether sudden variations following either an intentional experiment (of a dietetic, therapeutic, or physical nature) or an accidental occurrence indicate that the condition of the patient has been improved or impaired. Other symptoms will enable an experienced practitioner to decide that point with more certainty. Still, a careful use of albuminuria as a test in such cases must not be wholly discouraged.

Parenchymatous nephritis occupies a middle position. Protracted periods of marked and of slight albuminuria alternate with each other, and frequently, if not invariably, the general health of the patient is better when the albuminuria is considerable than when it is slight. The averages of these individual periods must be used with the greatest caution as tests of the intensity of the disease, and then only in association with all the other phenomena, which may help one in forming an opinion. Even more care is needed when a comparison is made of the quantity of albumin present in the urine at one moment with that excreted either previously or subsequently, and in using these rapid variations as a guide for therapeutic measures. I have records of over one hundred exact determinations of the albumin output in cases of parenchymatous nephritis. In some of these almost the same quantity of albumin was present in the urine day after day for a considerable length of time. In the majority of cases, however, in spite of perfectly uniform outward conditions (rest in bed, diet, intake of water, therapeutic treatment, etc.), great and unexpected variations occurred without any known cause; *e.g.*, the amount of albumin was increased or diminished by 50 per cent. or even more on several days. Thus, it is evident how easily we may be deceived if we assume uniformity of the albuminuria, and attempt, after investigations extending only over short periods of time, to estimate therapeutic results from changes in the amount of the excreted albumin.

The results are even more uncertain if, as often happens, only single samples of urine are examined, and not the mixed total daily output, for in every case the quantity of albumin varies from hour to hour, sometimes to an extraordinary extent, and these variations are not periodic. The following example illustrates this point:

Time.	*February* 15.	*February* 16.	*February* 17.
	Per Mille.	Per Mille.	Per Mille.
8 a.m. to 12 noon.	0·8	1·3	0·4
12 to 4 p.m.	2·3	0·8	1·9
4 to 8 p.m.	0·7	0·8	1·0
8 p.m. to 8 a.m.	1·2	0·5	2·0

Charrin has recorded similar changes (168), and everyone who has given attention to this subject could furnish other examples. Marked daily variations were formerly thought to be a characteristic of constitutional juvenile albuminuria, but they must now be recognised as occurring also in true nephritis [Daremberg and Moricz, etc. (169)].

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In view of the difficulties, it is quite comprehensible that the numerous authors who were anxious to determine the influence of diet—and especially of a protein diet—on albuminuria should have come to such very different conclusions (170). Some observers found that when the protein intake was considerable the albuminuria was unaffected, others that it was increased, and yet others that it was diminished. Some investigators observed that the albuminuria did not vary, others that it did vary in the different forms of Bright's disease. Even where the critic is prepared to make extensive compromises it is impossible to make any uniform generalization from these investigations. They have often led to the supposition that an increase or diminution of albuminuria is attributable to alterations in the diet, and yet it may very well be that they are to be reckoned amongst those unforeseen changes which ordinarily accompany this most variable disease. Some apparently definite results have been arrived at by methods which cannot be regarded as sufficiently accurate; others show quite clearly that in some particular case the albuminuria has not been increased by an increased intake of protein; others, again, to which practically no objection can be taken, obtain contrary results. Sometimes the increase of albuminuria persisted for only a few days, after which it fell to the former average. This fact, which I had met with before [von Noorden and Ritter (3)], and which has since been frequently described, shows how valueless are all investigations which only cover short periods of time.

After observations extending over twenty years it appears to me an established fact that in interstitial nephritis—the most important and frequent of all forms of kidney disease—the degree of albuminuria is in no way influenced by the protein intake.

In acute nephritis, on the other hand, and in the acute inflammatory exacerbations of chronic renal disease, a large protein intake undoubtedly exercises an injurious effect on the albuminuria. Even a milk diet is too rich in protein for this form of kidney trouble. When the inflammation is at its worst I give nothing but sugar-water (about 150 to 200 grammes sugar daily) and strained rice-broth, with cream or butter added. This régime reduces the work done by the kidneys to the lowest conceivable limit. I add milk to the diet only when the patient begins to be convalescent.

The diet in chronic parenchymatous nephritis should resemble that of granular kidney rather than that of acute nephritis.

Some authors maintain that in chronic albuminuria a moderate protein intake approaching the normal average cannot be considered responsible for any injurious results. But a harmful influence having been definitely established for the acute cases, we should naturally suppose that it would also operate, though more slowly, in the chronic forms of the disease. This conclusion, however, is not justified. It is frequently necessary to follow entirely opposite lines of treatment when dealing with acute and with chronic affections—*e.g.*, in acute diseases we try to keep the diseased organ passive (*Schonungstherapie*), whilst in chronic cases we keep it moderately active (*Uebungstherapie*); or, to put it in another way, in acute affections we concentrate our attention

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on the diseased organ, whilst in chronic cases we keep the general condition of the patient more in view. These principles apply also to the treatment of nephritis.

The question has recently been asked whether the various proteid bodies exercise an equal influence on albuminuria. As a rule, milk proteid appears to be the least harmful, and in the treatment of acute and chronic parenchymatous cases it is quite right to bear this fact in mind. Whether the same thing applies to interstitial nephritis has been much disputed, and in many quarters it is thought that the disadvantages of a milk diet [von Noorden, Pel, Grube, Kövesi and Roth-Schulz (171)] more than outbalance its supposed advantages as regards albuminuria. The old question as to whether a nephritic patient should be given red or white meat has also received closer examination. Neither the chemical composition of red and white meat [Offer and Rosenqvist, Walker Hall (172)], nor clinical experiment [Kaufmann and Mohr, Pabst, Wiczkowski, Kuschnir, Grube, Köster (173)] and clinical experience [von Noorden, Hale White (174)], appear to me to justify the main distinctions drawn between the two. The theoretical objections of Senator (175) on this point have been overcome [Offer and Rosenqvist, Offer (176)]. The prejudice which has found expression here and there against a fish diet in nephritis appears also to have been completely removed [Klemperer, Daremberg and Moriez (177)].

The course and severity of renal diseases, and especially of granular kidney, are much less influenced by subtle and artificial alterations in the diet than is commonly supposed. I am quite sure that the time will come when we shall allow our patients much more variety in their diet than is ventured upon by most physicians at present. The view will become general that many cases of chronic renal disease have suffered from the continuance of too one-sided a diet, and that it is much more important to maintain the patient's strength by mixed and varied food than to order a rigid diet in the hope that one may thereby reduce the excretion of proteids by a few decigrammes daily. The excretion of proteids is not a measure for the gravity of any case.

In acute and subacute cases Emerson (*Johns Hopkins Reports*, x., 1902) found a parallelism between the percentage of albumin and the temperature, both tending to rise with an unsuitable diet, or with an increase in the inflammatory process, or with exercise. The nature of the food was more important than the amount. For instance, a sweetbread sent up both the albumin and the temperature.

In connection with Loeb's (1580) investigations, Müller (117) raises the question whether an increase in the protein intake may not lead to an increased blood-pressure, and whether it is not to this fact, rather than to its doubtful effect on albuminuria, that the harm caused in renal disease by a protein rich diet is due. As yet there is not sufficient material to enable us to deal with this problem; but its solution is of importance, for Bier, Volhard and Krehl are quite right when they maintain that all therapeutic treatment must combat the causes of the condition, and not the raised blood-pressure itself, which in renal disease is a compensatory and necessary phenomenon.

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It is not yet wholly clear what these causes may be. From a clinical point of view the question is associated with that of the causes of uræmia. In France recently great importance has been assigned to retention of chlorides. Krehl also seems to incline towards this view, without recognising, however, that there is as yet no proof of its accuracy. As a matter of fact, there is considerable ground for doubt, for it is in cases of parenchymatous nephritis with œdema that retention of chlorides occurs most frequently, together with a blood-pressure which, on an average, is much lower than in typical granular kidney, whilst in this latter disease an appreciable retention of chlorides only occurs in the final stage.

Further, it is to be borne in mind that in acute nephritis the rise in blood-pressure sets in extremely early, before any considerable retention of chlorides has taken place. Riegel demonstrated this some time ago by the aid of the sphygmograph, an instrument which may be productive of many errors in the hands of an unskilled operator, but which gives reliable results when used by a competent investigator (170B). The same condition was found by my assistant, Schliep, in a case of scarlet fever. He made daily estimations of the blood-pressure by means of the Riva-Rocci apparatus after the initial fever had disappeared—*e.g.*:

Case and Date.	*Blood-pressure.*	*Remarks.*
Male, aged nine years:		
1905—March 5	60	
„ 12	70	No albuminuria.
„ 23	100	
„ 26	120	
„ 30	120	On March 25, hæmorrhagic nephritis with uræmic symptoms.
April 4	100	
„ 13	75	Recovery.
Female, aged nineteen years:		
1905—March 23	80	
„ 25	65	No albuminuria.
„ 29	60	
April 4	70	
„ 13	115	
„ 14	145	
„ 15	120	Nephritis commenced on April 13. At end of April only traces of albumin. May 31, recovery.
„ 16	120	
„ 17	100	
„ 18	110	
„ 19	120	
„ 23	100	—
„ 29	90	—
May 3	75	—
„ 4	80	—
„ 17	80	—

This extraordinarily rapid reaction of arterial tension to renal disease is closely associated with the much-discussed question as to whether substances as yet unknown pass into the blood and lead to an increase

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of arterial pressure, thus contributing to the general effect produced by those extractives of metabolism which are ordinarily retained by the diseased kidney or by other organs (" chemical reflex," suprarenal).

E.—TOXINES OF THE URINE.

Bouchard considers that he has experimentally proved that a healthy person produces every twenty-four hours an approximately constant amount of urinary toxines per kilogramme of body-weight (178). He goes so far as to estimate a definite percentage of toxic effect for each individual constituent of the urine—water, salts, pigments, urea, organic bases, etc. He proceeded to determine by experiment how many cubic centimetres of urine injected intravenously were necessary to kill an animal (rabbit), and expressed this in terms of the weight of the animal. From this he deduced the toxine production of the individual per diem and per kilogramme (" toxine coefficient ".) One of the first and most important conclusions he established was the diminution of toxic effects in renal disease, and especially in uræmia. He concluded from this that, in consequence of the incapacity of the kidneys, the body does not excrete, but retains, both the poisonous products of metabolism and those toxic bodies which are absorbed from the intestines. This retention he regards as the cause of uræmia and of death. Unfortunately, the method of this gifted investigator has not fulfilled all that it promised. The results of the experiment depend upon so many factors—one might say even upon so many chances—that even the most careful procedure cannot ensure uniform results. Many physical and chemical factors which had nothing to do with the uræmic intoxication undoubtedly contributed to the death of the animal injected with urine. It is only an extremely poisonous or a non-poisonous state of the urine that is worth consideration. It is certainly not necessary to make use of this elaborate method in order to prove auto-intoxication in cases where there is a diminution of the toxines in the urine, accompanied by lessened excretion, or far-advanced nephritis, or general uræmic symptoms. But even in these cases the method often fails. Instances have been described by experienced observers where, in spite of obvious uræmia, Bouchard's method showed a high toxic value of the urine [Bernard (179)]. Apart from extreme cases, which are of little interest from the point of view of diagnosis and prognosis, the method has not helped us to arrive at a quantitative determination of the elimination of poisons. In spite of many adherents, belonging mostly to the Bouchard school, the method has been subjected to severe criticism (180). I am in full agreement with Ewald and Ascoli, who in a recent critical study, and in spite of the contention of Claude and Balthazar (182), express the view that Bouchard's proposal is unsatisfactory as a test for determining the incapacity of the kidneys or the retention of toxines, or as affording theoretical insight into the nature of uræmia. I expressed a similar view more than twelve years ago in my text-book on "The Pathology of Metabolism." In certain medical circles, however, and especially in Paris, the theory of the " urotoxic

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coefficient" is awarded a high place, and whether toxic retention is present or not, no analysis of nephritic urine is considered complete which has not been obtained by estimating this coefficient. This can only be regarded as pseudo-scientific humbug, which has nothing in common with the atmosphere of scientific seriousness which surrounded Bouchard's painstaking studies.

F.—FOREIGN SUBSTANCES.

The metabolic disturbances characteristic of nephritis are expressed in the insufficient elimination of urinary substances. This is true, not only of the particular disintegration products of metabolism, but also, and perhaps to an even greater degree, of substances which do not usually come into contact with the kidneys. This fact has long been known, and is a most important one for the medical man. Often, however, it is not sufficiently taken into consideration. Hence it may happen that drugs, even if given in small doses, will produce toxic effects. Instead of leaving the body at the proper moment, and making room for subsequent doses, they accumulate in the fluids and tissues. Heavy metals—especially mercury—and alkaloids are the worst in this respect. This question cannot here be considered in detail; it belongs rather to clinical and pharmacological text-books.

The difficulty of excreting certain substances in renal disease has also been made to serve for purposes of diagnosis, and as a guide for the quantitative estimation of renal incapacity. For instance, a patient was given a small definite quantity of potassium iodide, and the time of its appearance first in the urine recorded. As compared with that of healthy persons, this reaction was often considerably delayed. It seems that Wolff was the first to make use of this method as a means of determining and estimating renal incapacity (182A). Recently it has also been employed by Müller (117). I discontinued some investigations which I made in Riegel's clinique in 1885 upon twenty-five cases of renal disease because of the great irregularity in the iodide elimination, and because no obvious parallel existed between its excretion and that of the normal products of metabolism. The delay in the elimination of iodide in extreme cases is certainly most striking.

A healthy person, after taking 0·2 gramme iodide in a gelatin capsule, will show a reaction within ten to twelve minutes in both urine and saliva. As a rule, this lasts for about twenty hours, and seldom more than thirty-six hours. In nephritic patients the salivary reaction occurred after an almost normal interval; sometimes, however, it was retarded in a very striking manner—ten to fifteen minutes. Iodide was often found in the urine only after forty to sixty minutes had elapsed, sometimes only after two to four hours. The positive reaction in both urine and saliva lasted sometimes from four to six days.[1]

[1] As I long ago remarked elsewhere, iodine is found in combination with albumin—partially, at all events—in cases of continued albuminuria. In many cases no reaction is obtained by the use of hydrochloric acid, whilst the treatment of the urine with freshly-prepared chlorine solution sets the iodine free.

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Other and more easily recognisable substances have recently been preferred for purposes of experiment, such as methylene blue or indigo carmine. The most reliable of all appears to us to be the salicin test, the relations of which to both the healthy and the diseased kidney have recently been investigated by Schliep. Even this did not always give accurate results. Exceptions prevailed which set all known rules at defiance. I have already stated elsewhere that great uncertainty is attached to all these methods, and that retention of even the most important extractives of metabolism is in no way parallel to that of drugs and pigment [von Noorden (182A)]. Besides, one finds in cases of nephritis that the excretory capacity presents very wide differences according to the drugs used. I do not think that these tests will be much more employed in our diagnosis of bilateral renal disease. On the other hand, if every precaution is taken against all possible sources of error, they appear to be useful for comparing the secretive capacity of one kidney with that of the other. The investigation of the excretion of pigment by the cystoscope is simpler, quicker, and more effective than chemical analysis of the separated urines.

For a study of the special conditions accompanying phloridzin-poisoning, see a later section of this chapter, and also the chapter on the Pharmacology and Toxicology of Metabolism in the third volume.

V.—INFLUENCE OF RENAL DISEASE ON THE BLOOD.

From the earliest days of biochemical investigation the composition of the blood in renal disease has been a subject of the greatest interest to numerous inquirers. It was here that a search was made for the substances which the diseased kidney was either unable to get rid of or only excreted with difficulty, and it was hoped that the chemistry of the blood in nephritis would solve the question of the character and causation of uræmic intoxication. These hopes have been to a large extent, although not entirely, fulfilled.

A.—CONCENTRATION OF THE BLOOD.

It has long been known, especially since the researches of Christison, Becquerel, and Rodier and Schmidt (183), that the blood of nephritic patients is frequently characterized by a low specific gravity and an increased water content. But it is only in the last ten years that its changes in various forms and stages of the disease have been discovered.[1]

We must take first into consideration the fact that abnormal dilu-

[1] It is not necessary to consider here either the numerous individual investigations, or the isolated remarks on this subject which are to be found in many communications, since all are in practical agreement. No. 192 in the Literature index indicates the most important publications. In conjunction with these the reader should consult H. Strauss's communication on the influence of chronic renal disease on the blood: "Die chronischen Nierenentzündungen in ihrer Einwirkung auf die Blutflüssigkeit," Berlin, 1902. I shall have, however, frequent occasion to controvert his conclusions.

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tion of the blood, when present, affects the plasma in an important and typical way, whereas the blood-corpuscles continue to maintain their normal content of solid substances. Although the investigations of Frerichs (184), and later of Hammerschlag, Biernacki and Askanazy (185), indicated this fact, the first reliable proof was established by Kössler (186), who employed more reliable methods. This alteration in the blood is identical with that which was formerly expressed by the term "hydræmia," a word which has since been erroneously used to express other abnormalities of the blood, such as a simple diminution of the blood cells. It is certainly true that, whether hydræmia is present or not, a diminished number of red blood-corpuscles and of hæmoglobin frequently occurs in the blood of nephritic patients—the phenomena, that is, of ordinary so-called anæmia. This is not to be wondered at, for loss of blood through the kidneys involves insufficient nutrition, complications of the most varied kind, digestive disturbances, and other unfavourable conditions which fully account for the unsatisfactory state of the blood [Askanazy, Kössler]. When the predisposition of nephritic patients to true hydræmia has been established, it is necessary in every case to test the concentration of the serum in order to form a true opinion concerning the hæmoglobin and erythrocytes. It is only by this method that one can decide whether an apparent slight decrease in the percentage of corpuscles and pigment indicates their real diminution, or whether it is only the result of hydræmia—*i.e.*, dilution of the blood. The latter explanation is certainly the true one for many of the older investigations [Leichtenstern, Laache, Reinert (187), etc.]. On the other hand, the exhaustive analyses of Schmidt, Askanazy, Kössler, Hammerschlag, Biernacki, von Jaksch, Benczur and Czatary, Dieballa and von Kétly, Wendelstadt and Bleibtreu (188), and others, show, as has been already remarked, that true anæmia may accompany hydræmia.

Where œdema is developed in acute nephritis the concentration of the blood is almost invariably lessened (189). As a rule, the cause of this appears to be hydræmia—that is, dilution of the plasma—so that values of 1018 to 1022 for the specific gravity of the serum (instead of 1027 to 1032) are often met with. Not a few cases, however, occur in which previous infection, intoxication, or other injurious influences have diminished the number of corpuscles and reduced their hæmoglobin content. It is only in cases of persistent œdema, however, that hydræmia is invariably present in the serum. Neither the proportional relations between œdema and nephritis, nor those which exist in the other forms of acute renal disease, have as yet been determined (190). Where, as not infrequently happens, acute nephritis is not accompanied by thirst, hydræmia, as a rule, is also absent—*e.g.*, in acute sublimate-poisoning. After a perusal of the numerous communications on this subject, I am convinced that Senator is right when he maintains that hydræmia is never found in acute nephritis unless it is accompanied by thirst (191). This is of importance from a theoretical point of view, as it throws doubt on the hypothesis that hydræmia is the cause of nephritic œdema (see below on Œdema).

Hydræmia is a much more frequent symptom in cases of parenchy-

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matous nephritis—which is almost invariably accompanied by varying degrees of œdema—than in cases of acute renal disease. All authors are agreed on this point (192). The specific gravity of the serum varies from 1018 to 1023, and the amount of water from 94 to 92 per cent. (normal, 89 to 91 per cent.). The percentage number of corpuscles, the hæmoglobin, the specific gravity, and the dry substances of the blood are also diminished. In severe and prolonged cases these values undergo, for the most part, greater alterations than can be accounted for by the dilution of the plasma. It must, therefore, be assumed that anæmia, as well as hydræmia, is present. Cases, however, have been seen in which the increase of water in the serum was sufficiently great to account for the other alterations in the concentration of the blood. Generally speaking, the variations of œdema and of hydræmia run parallel to one another, though even this cannot be regarded as an invariable rule [E. Reiss (193)]. It is important to emphasize here the contrast between the œdema of nephritis and that of congestion. In the latter condition the concentration of the blood, and especially of the serum, is not so far removed from normal as is the case in nephritis, especially when anæmia is present. It is thus evident that in nephritis hydræmia is caused by other than purely mechanical conditions.

In lardaceous disease of the kidneys hydræmia is always present, and is accompanied by anæmia.

The conditions are different in intestinal nephritis without œdema. The number of corpuscles, the amount of hæmoglobin, and the specific gravity of the blood often remain normal, especially during those long periods which are described as "compensated granular kidney," when the patient is in relatively good health. In far advanced cases, however, after patients have begun to be affected by cachexia and anæmia, the concentration of the blood is somewhat lowered. True hydræmia, however, is exceptional, and is developed only when uræmia and failure of compensation set in, and when œdema appears. In such cases there is severe impoverishment of the hæmoglobin and corpuscles of the blood [Laache, Leichtenstern (187)], together with hyperalbuminosis—*i.e.*, hydræmia—of the serum. Hence a very marked dilution of the blood frequently occurs [Biernacki (185)].

B.—MORPHOLOGY.

The morphology of the blood in nephritis does not undergo any typical alteration [Grawitz, von Limbeck, Pieraccini (194)]. The red blood-corpuscles are not degenerated. Where striking anomalies do exist, they are dependent on the numerous complications which accompany nephritis rather than on the renal inflammation itself [Schur and Loewy (195)]. It is only in acute nephritis, especially when it occurs in childhood, that the leucocyte count is increased [Bogdanow-Beresowsky, Rohde (196)]. Müller and Rieder found normal values for the eosinophile cells; Zappert (196A) recorded an increase to 5 per cent.

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C.—ALKALINITY.

Where renal disease is not attended by complications, and no uræmic symptoms are present, the alkalinity of the blood remains normal [von Jaksch, Strauss, Brandenburg (197)]. In some cases, indeed, high values have been recorded [De Renzi, Loewy (198)]. On the other hand, all authorities are agreed that the alkalinity undergoes considerable diminution directly uræmia supervenes. It is only in diabetes and severe fevers that such high values occur as are found in uræmia. This fact was observed by von Jaksch (197), and has since been frequently confirmed, with more or less insistence, by many other observers (199). The figures of each author must be considered separately. Comparison is impossible, because different methods were used in almost every case. The following examples illustrate the point:

Burmin: Healthy persons showed in 100 c.c. of blood an alkali value of 182 to 218 milligrammes NaOH; in a uræmic patient the alkalinity amounted to 92 milligrammes (Laudois' method).

Brandenburg: Healthy persons showed in 100 c.c. of blood an alkali value of 300 milligrammes NaOH. Of this, 20 per cent. was diffusible, and not in combination with proteid substances. In a uræmic patient the alkali value amounted to 192 milligrammes NaOH, and 20 per cent. of this also was diffusible (Loewy's method).

More recent investigations have shown that alkalinity to a great extent is dependent on the concentration of the blood, and especially on its proteid content. In view of this, attention must be drawn to the fact that the nitrogen found in the blood of Brandenburg's uræmic patients was very much less in proportion to its alkalinity than was found to be the case in health or in non-uræmic renal patients.

As is well known, all determinations of the alkali in the blood are, to some extent, doubtful, for we have not as yet discovered a perfectly satisfactory method for conducting these tests [H. Friedenthal (200)] (see Gamble, *Journal of Pathology*, 1906). Still, it can hardly be doubted that uræmia is accompanied by a high degree of acidity in the blood. The question is whether (as von Jaksch supposes) this excess of acidity has an etiological significance in regard to the general symptoms of uræmia. I do not consider that this is established, and should here point out that the acidity of the blood in diabetes mellitus is more marked and more persistent than in uræmic patients, although it produces no phenomena similar to those of uræmia. It is very doubtful whether the small amount of uric acid which can be definitely ascertained as present in the blood of renal patients, or the questionable presence of lactic acid [Gottheimer (201)] and of carbamic acid [H. Winterberg (202)], can be adduced in support of the theory. On the other hand, I must remind the reader how readily bodies belonging to the β-oxybutyric series accumulate in the blood of uræmic patients. As a rule, for days together both solid and liquid food is vomited, and as soon as uræmic symptoms set in the condition of the renal patient is similar to that of a person suffering from hunger, or, at any rate, from a marked degree of inanition.

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Very often the urine reacts to chloride of iron. I wish to emphasize the fact that one must first exclude inanition as the cause of the accumulation of acetone bodies in the blood before it is possible to consider whether uræmia may not be a special form of acid-poisoning.

D.—THE NON-PROTEIN NITROGEN OF THE BLOOD AND OF ŒDEMA.

This " non-proteid nitrogen " was formerly termed " extractive nitrogen," but recently the name " retention nitrogen " has been introduced by Strauss (203). I do not think this a happy expression, because in 100 c.c. of normal blood-serum (average nitrogen content, 1·3 per cent.) 20 to 35 milligrammes of nitrogen is not in combination with proteid substances (1·5 to 2·5 per cent. of the total nitrogen). It is not justifiable to say that these amounts are " retained," for there is no doubt that some portion of them play an exceedingly important part not only in the disintegration, but also in the synthesis of complex nitrogenous substances (albumins, proteids, etc.), and also in effecting the transference of other non-nitrogenous combinations from one part of the body to another (*e.g.*, sugar and fats). It is only when unusually large quantities are present that the difference between the analytical and the normal values can be logically described as " retention nitrogen." The expression " filtrate nitrogen," on the other hand, does not involve any, or hardly any, assumption.

The most important constituent of this filtrate nitrogen is urea. Strauss is probably right in estimating urea as forming at least one-half, and perhaps even four-fifths of the total nitrogen. The values that have been determined for filtrate nitrogen hold good also, with a few limitations, for urea, and *vice versa*. Strauss affirms that a far-reaching parallelism exists between the filtrate nitrogen of the blood or serum, on the one hand, and that of the transuded œdematous fluid on the other hand. This is easy to understand, since these fluids are in a state of continuous osmotic exchange.

1. Total Filtrate Nitrogen.

In view of what has been already stated, the urea and the total filtrate nitrogen may be considered simultaneously, although they are not, of course, identical. The older investigators refer to the fact that an increased amount of urea is present in the blood of nephritic patients (204). Values of 100 to 200 milligrammes are stated to be often present in 100 c.c. of blood ; Bartels mentions as much as 373 to 663 milligrammes of filtrate nitrogen.[1] On the other hand, many estimates, obtained under similar clinical conditions, exceed the normal by only very slight amounts, and sometimes fall below it by 1 per cent.

Recent investigators, who have had better methods at their disposal, have concentrated their attention more exclusively on the total filtrate

[1] An enumeration of these communications has been compiled by Strauss, and also by Ascoli (3).

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nitrogen, the urea being only ascertained by special determinations. The earlier chemical analyses of the blood of nephritic patients, and the investigations of von Noorden and Ritter (3) into their nitrogenous balance, indicated that no definite relation exists either between retention of nitrogen on the one hand, and the gravity of the disease on the other, or especially between such retention and the presence or absence of uræmia. The results of more recent examinations of the blood [Ascoli, Strauss, Bottazzi and Pierallini, Landau and von Jaksch] confirm and support this conclusion (205). As Ascoli, who employed similar analytical materials, has already demonstrated, it appears that, although the quantity of filtrate nitrogen is greater in renal disease than in other diseases or in health, and that the highest values are, as a rule, most frequently present in uræmia, yet, on the other hand, cases of nephritis often show normal or almost normal values. Occasionally, however, lower values are present in cases of uræmia, while sometimes the figures are quite high where there is no uræmia. The last condition is especially likely to occur in cases of complete anuria with or without nephritis. An instructive example of this has recently been investigated by Umber (206). Anuria had been present for eighty hours; the blood contained 0·138 per cent. filtrate nitrogen; there was no uræmia. Where sublimate-poisoning with anuria was present without uræmia or œdema, I found on the third and fifth days of the anuria 0·142 and 0·189 per cent. filtrate nitrogen. Just as the investigations of Frerichs, and later those of Landois (207), showed that uræmia is not to be regarded as urea-poisoning, so it can be affirmed that neither is it dependent upon the total filtrate nitrogen of the blood. This is also true of the nitrogenous extractives contained in the tissue fluids, since these, as has already been remarked, correspond to the filtrate nitrogen of the serum.

Strauss describes a difference between the behaviour of the filtrate nitrogen in parenchymatous and in interstitial nephritis. In the former a small, and in the latter a large amount of "retention nitrogen" is present in the blood (normal, 20 to 35 milligrammes in 100 c.c. blood-serum).

Disease.	*In the Blood-serum (without Uræmia).*	*In the Blood-serum (with Uræmia).*
	Per Cent.	Per Cent.
Interstitial nephritis (average)	0·0822	0·1297
Parenchymatous nephritis (average) ..	0·0397	0·0623

Although I do not wish to express the least doubt as to the accuracy of these analyses, I do not think that they indicate the existence of any characteristic difference. In the first place, very high values are often present in cases of typical parenchymatous nephritis. Strauss himself records that the highest value he ever met with in non-uræmic patients (0·152 per cent.) occurred in a case of parenchymatous nephritis; whilst, under similar conditions, the maximum value for interstitial nephritis

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reached only 0·116 per cent. Further, it must be remembered that the majority of patients with parenchymatous nephritis suffer from both hydræmia and œdema. More dilute blood naturally contains fewer solid constituents, besides which the accumulated nitrogen tends to become widely diffused in the œdematous fluid. At all events, because the percentage of filtrate nitrogen is, on the average, lower, the conclusion cannot be drawn that retention of nitrogen plays a less important part in parenchymatous than in interstitial nephritis. The figures of the nitrogenous balances would rather suggest the contrary. Finally, it may be pointed out that, as a rule, cases of parenchymatous nephritis take less food, and especially less proteid food, than do cases of interstitial nephritis. Whether further critical inquiry will establish it as a fact that, given similar conditions (similar food, absence of œdema, or a similar degree of hydræmia and œdema), the blood and tissue fluids in parenchymatous nephritis accumulate less filtrate nitrogen than in interstitial nephritis is an open question. However this may be, the far-reaching conclusions of Strauss (208) regarding the prognosis and therapeutics of nitrogen retention do not carry conviction. For, in contradistinction to the gloomy picture he draws, it may be remarked that retention of nitrogen within the limits which are usually present in cases of interstitial nephritis is not dangerous. Practical clinical experience undoubtedly shows that interstitial nephritis is a disease which may last and be well borne for very many years, whilst parenchymatous nephritis, where it does not pass into granular kidney and so become relatively cured, results in death within from six to eighteen months.

It is interesting to estimate how much filtrate nitrogen may accumulate in the blood and tissues. The results of investigations into the metabolism of renal disease have already made this possible. In a case of typical chronic parenchymatous nephritis I found in 35 litres of œdematous fluid, drawn off within five days, 0·190 per cent. of filtrate nitrogen—that is, nearly 70 grammes of nitrogen. I would here point out to any investigators interested in this question that the composition of the œdematous fluid in any one particular case is not uniform, either in all parts of the body or at successive periods—*e.g.*:

Chronic Parenchymatous Nephritis.	*Filtrate Nitrogen*—	
	Right Leg.	Left Leg.
Case I.:	Per Cent.	Per Cent.
June 26	0·0928	0·0840
„ 27	0·0897	0·0792
July 23 (second puncture) ..	0·0716	—
„ 24	—	0·0710
Aug. 26 (third puncture); uræmia	0·0144	—
Sept. 27 (fourth puncture).. ..	0·0748	—
Case II.:		
Jan. 3	0·1100	0·1262
„ 4	0·0978	0·1173
„ 4	0·0654	0·0731
„ 5	0·0460	0·0471

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Although the filtrate-nitrogen values of nephritic blood vary to an extraordinary extent, and although they do not exhibit any relation to the gravity and immediate danger of the case, or to the degree of uræmic intoxication, still, it cannot be doubted that the accumulation of the nitrogenous products of metabolism occupies an important position amongst those phenomena which are the result of renal incapacity. It is possible that future investigations may show a more direct and simple relation between the filtrate nitrogen content of the fluids and the degree of nitrogen retention indicated by the metabolic balance. Up to the present time, however, the determinations of these two values have only corresponded in a very few cases. If, as appears probable, this supposed relation is not established, it should be remembered that not only the tissue fluids and the blood, but also the cell elements of the tissues, form a large reservoir for the absorption of extractives. As a matter of fact, accumulation here takes place sooner than in the blood [R. Rosemann (125)]. To what extent, and for how long, the nitrogenous and other extractives (*e.g.*, salts) in the tissues can become fixed and neutralized is not yet known. At all events, the existence of this extensive reservoir makes it impossible to determine, as we otherwise conveniently could, by analysis of the blood (determination of filtrate nitrogen or cryoscopy), the degree of retention and the danger of poisoning by extractives. Before this can be done it will be necessary to establish the conditions which determine their distribution between the tissues and the fluids respectively.

2. Individual Nitrogenous Substances.

(*a*) *Urea and Amido-acids.*

Some investigations have been made in order to determine the amount of urea nitrogen present in the total filtrate nitrogen (209). The figures of Umber and von Jaksch show that, on an average, 89 per cent. of the filtrate nitrogen consists of urea ; Strauss gives his average as 75 per cent. (in the ascitic and œdematous fluid of the nephritic patient). Ascoli estimates that, on an average, 0·1034 per cent. of filtrate nitrogen is present, and his results agree with those of Strauss in showing that 75 per cent. consists of urea and monamido-acids. If we exclude the somewhat doubtful quantitative separation of urea from the monamido-acids, and estimate as urea all nitrogen which cannot be precipitated by phospho-tungstic acid, we approximate very closely to the correct values. The statistics given above fulfil these conditions.

(*b*) *Uric Acid.*

Sir A. Garrod demonstrated the presence of uric acid in the blood of renal patients [0·3 to 3·7 milligrammes in 100 c.c. of blood (211)]. More recently von Jaksch has found it in the blood of healthy persons, and also in patients suffering from a variety of diseases (212). In

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nephritis, however, the quantity was considerably greater, especially when there was a predisposition to uræmia, or when it was actually present. Von Jaksch has been able to set aside the objections raised by von Fodor (213), and to confirm his statement by fresh evidence. The investigations of Klemperer, Magnus-Levy, Pickardt, Petrén, Strauss, and Umber, made partly on the blood and partly on the transudates and œdematous fluid, have confirmed the results obtained by Garrod and von Jaksch (214). The values vary, for the most part, from 1½ to 3 milligrammes of uric acid in 100 c.c. of blood (normal, 0·3 to 0·6 milligramme), rising sometimes to 6 milligrammes or more. There does not appear to be any special relation between the presence of this acid and uræmia, for similar, or considerably higher values are found where there is no trace of uræmia, in acute fevers (pneumonia), in leuchæmia and gout, and also in healthy persons on a diet rich in nuclein. It has already been stated that uric acid is, on the whole, one of the substances easily excreted by nephritic patients. The condition of the diseased kidney, however, does not allow of its transmission from the blood in normal quantities; hence its concentration in the blood is above the usual average (see chapter on Gout).

Nothing definite is known as to the presence of other purin bodies in the blood of patients suffering from kidney diseases.

(c) *Ammonia.*

For a considerable time, and owing to the influence of von Jaksch senior, Treitz and Frerichs, the ammonia content of the blood was thought to be important in determining the occurrence of uræmia. Frerichs stated that it was formed from urea by fermentation, and circulated in the blood as ammonia salts. Later investigations made it seem probable that it was combined with the protein substances of the blood [Rumpf (216)]. The older theory of von Jaksch and of Frerichs has long since been abandoned (217), and recent analyses, conducted with improved methods, have shown that sometimes, but by no means invariably, the ammonia in the blood of renal cases exceeds the normal amount—about 0·6 to 1·3 milligrammes in 100 c.c. blood [Winterberg (218)]. However, it does not appear that the accumulation is so great as to produce toxic effects [Winterberg, Ascoli (219), Strauss (203)]. In three patients with uræmic coma, Winterberg found 2·06, 1·91, 2·15, and 0·68 milligrammes of ammonia, whilst two non-uræmic renal cases had 0·87 and 1·42 milligrammes in 100 c.c. of blood. Strauss gives rather higher figures, the average in parenchymatous nephritis being 2·5, in renal cirrhosis 5·2, and in transition stages 3·6 milligrammes. If still higher values occasionally occur in cases of uræmia accompanied by diarrhœa, it must be attributed to absorption of the NH_3, which is present in such large quantities in the fæces. Ammonia is attracted to, and fixed in the nervous tissues, and especially in the cerebral cortex, yet in renal disease the amount of ammonia contained in nervous tissue is not much above the normal [Salaskin (220)]. The extremely toxic effects of these

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ammonia combinations have recently been again pointed out by Rumpf (221). The question as to whether or no they are responsible for the auto-intoxication of renal cases I cannot as yet consider as settled, although it is hardly probable that the theories regarding the ammoniæmia of uræmic cases can ever be revived in their old form.

(*d*) *Creatin.*

Some of the older observations (analyses) record an increase of creatin in the blood of nephritic patients [Schottin, Hoppe, Oppler (222), Perls (223)], and also that a quantity of this substance was found in the muscles of persons who had died from uræmia. From this fact Jaccoud (224) formulated his theory of creatinæmia, which he regarded as the most important factor in uræmic intoxication. Later, Landois demonstrated that creatin produced convulsions and coma by direct action on the cerebral cortex (207). It has, however, rightly been contended that creatin never accumulates in sufficient quantities to cause poisoning (225). Gautier has raised the question as to whether creatin becomes transformed in cases of uræmia into methyl-guanidin, which is excessively poisonous. Traces only of creatinin, which is far more poisonous in its effects than creatin, are met with in the tissues.

E.—MINERAL SUBSTANCES.

1. Potassium Salts.

The retention of potassium salts in cases of kidney disease roused more interest than that of any other mineral substance when Feltz and Ritter, Astaschewsky, and, with certain reservations, Rovighi, Roger and D'Espine, attributed the development of uræmic symptoms to its action (227). This theory, however, has long ago been given up, for a closer study of the toxic effects of potassium salts has shown that they differ absolutely from the general features of uræmic intoxication [Landois, Bouchard (228)]. Also, the numerous potassium analyses of nephritic blood do not show that any abnormal amount is present (229). The figures vary, as a rule, from $1\frac{1}{2}$ to $2\frac{1}{2}$ per cent., and are consequently within the normal limits.

2. Chlorides.

Attention has been recently directed more closely to the chloride contents of the blood and of the œdematous fluid. This is due to the fact that Bohne has suggested that chloride retention bears a direct relation to uræmia (107), whilst Widal maintains that it is connected with the formation of œdematous fluid (109). The numerous analyses of the blood and serum yield no decisive results, either as regards the nature or the stage of the disease (230). Runeberg gives the normal value of sodium chloride for the serum as 0·58 to 0·67 per cent. The figures obtained from

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analyses of nephritic blood usually equal these amounts, but in some cases abnormally small quantities are found (*e.g.*, by Biernacki, Bruner, Dennstedt, and Rumpf), although it frequently happens that the values slightly exceed the normal average [von Limbeck, Koranyi, Strauss, Halpern]. The presence of uræmia was not found to affect the figures—*e.g.*, the amount of NaCl in the serum in four cases with uræmia varied from 0·507 to 0·630 per cent.; in three cases without uræmia from 0·580 to 0·682 per cent. [Strauss]. The percentage of NaCl in the serum is, of course, no guide in determining to what extent accumulation of sodium chloride has taken place, for, on the one hand, the hydræmic condition of the serum may conceal the increase of sodium chloride, and, on the other hand, the tissues may take up a great deal of NaCl. It is easy to understand this in cases where œdema is present. According to Strauss's comparative determinations, it appears that œdematous fluid always contains rather more NaCl than serum. The difference amounts to from 5 to 7 per cent. But even where there is no œdema the tissues may store up a large quantity of NaCl, as is shown by the NaCl balances of non-œdematous nephritic cases. Marie has recently shown that this is also true of healthy persons (118). He found that a healthy individual, on a diet containing an excess of chloride, accumulated 92 grammes NaCl in twelve days, and that 15 litres of fluid were required to dissolve it. The body-weight, however, was only increased by 1,200 grammes. From these figures Marie concluded that two modifications of NaCl exist in the body—that is, *chlorure fixée*, which does not produce œdema, and *chlorure libre*, which attracts water, and produces œdema by osmotic exchange with the blood. In view of the theoretical and therapeutic interest which has recently centred on chloride retention in nephritis—an interest which I cannot but consider as somewhat exaggerated, one-sided, and superficial—it is much to be desired that new estimations should be made as to its presence in the blood and tissues. We have to thank Rumpf (229A) for a preliminary inquiry into this subject. It is not apparent from his figures, which, however, are somewhat scanty, that there is any close connection between chloride retention and œdema.

F.—THE FREEZING-POINT AND ELECTRICAL RESISTANCE.

1. Lowering of the Freezing-point.

The freezing-point of the blood is necessarily lowered when the excretion by the kidneys of the extractives of metabolism is insufficient, and there is no simultaneous alteration in the quantity of water contained in the blood. The determination of the freezing-point gives more reliable evidence as to the concentration of these extractives than either the specific gravity or the dry substances, since these are influenced by the protein content. The normal lowering of the freezing-point of the blood-serum (δ) is from $-0{\cdot}55°$ to $-0{\cdot}59°$, usually from $-0{\cdot}56°$ to $-0{\cdot}57°$; in healthy persons these figures are steadily maintained. The

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first investigations of Koranyi (231) and of Lindemann (90) make it seem probable that the determination of the freezing-point of the blood or blood-serum would afford a valuable, and above all a reliable, test of the degree of renal incapacity in any particular case. The method acquired special importance from a surgical point of view, for in cases where, presumably, only one kidney was diseased a normal freezing-point would indicate that the other was functionally sound, and that, therefore, the removal of the affected organ was permissible [Rumpel, Kümmell (232)]. Since then Loeb and Adrian have recorded that, in cases of unilateral renal disease, a higher molecular concentration of the blood is occasionally present (133). At the last Surgical Congress many objections were raised against the theory (103A).

Although it must be conceded that cryoscopy of the blood promises more trustworthy results than the much misused and overrated cryoscopy of the urine, yet the theories originally laid down will undoubtedly have to undergo considerable modification. The enormous literature on the subject has been very thoroughly discussed by Strauss (234). The communications of Haussen and Grünthal, Kövesi and Roth-Schulz (235), deserve especial mention on account of the careful criticisms they contain. The results obtained from the above-mentioned works are as follows :

Increased molecular concentration (from about $\delta = -0{\cdot}63°$ or lower) is always a sign that the kidneys are not acting as they should, except where special and easily recognisable conditions prevail, such as severe loss of fluids from the body and long-continued thirst.

The molecular concentration of non-uræmic renal patients is, as a rule, only slightly raised. It is seldom that the lowering of the freezing-point exceeds $-0{\cdot}61°$. Such cases as these are sufficiently frequent to controvert the contention of Lindemann and Couvée that the alterations of osmotic pressure have an etiological relation to uræmia. That a high molecular blood-pressure makes the exchange of substances between the blood and the tissues, and also the elimination of the waste products of metabolism, more difficult must be admitted, and that this hindrance to excretion may favour uræmic auto-intoxication cannot be denied, but at the same time it must be pointed out that an increased molecular pressure cannot be held responsible for uræmia in any other sense than as a predisposing cause.

It much more frequently happens that the osmotic pressure, so far from being abnormally raised, is quite normal, even in cases in which no doubt can be entertained as to the existence of a considerable degree of retention of extractives. Landau (205), and before him Koranyi (231), have rightly pointed out that hydræmia (dilution of the serum by water) militates against such retention. This may account for the fact that the osmotic pressure of the serum in parenchymatous nephritis is usually found to be rather lower than in interstitial nephritis.

The figures for the molecular concentration in uræmia are, for the most part, very much higher. The freezing-point often falls to $-0{\cdot}70°$ and $-0{\cdot}75°$, or even lower. This lowering is usually more noticeable in cases of granular kidney than in patients suffering from parenchymatous

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nephritis, obviously because the latter develop severe hydræmia together with uræmia. On the other hand, uræmic patients may show normal or nearly normal values [*e.g.*, Koranyi, Rosemann, Poly (237)].

The confirmation of these facts permits the statement that any considerable increase of osmotic pressure is significant both as regards semiology and prognosis, but that normal lowering of the freezing-point is not incompatible with severe, or even the severest degree of renal disease, nor—and this is especially important—with the retention of waste products. In explanation of this remarkable fact, it must be borne in mind that the tissues themselves form an extensive and favourite reservoir for the reception of the waste products of metabolism [Rosemann (125)].

In those cases in which the blood-serum and transudates (pleural, abdominal, subcutaneous) have both been investigated, the osmotic pressure of each has been found to be equal to, or rather less than, that of the blood [Ascoli, Ceconi and Micheli, Strauss (238)]. Sometimes, however, remarkable variations occur, which may be above or below the normal average. There is as yet no satisfactory explanation of these [L. von Kétly and A. von Torday (239)].

2. Electrical Resistance of the Blood-serum.

A comparison of the lowering of the freezing-point with the electrical resistance gives the content in the serum of non-electrolytes and electrolytes ; the latter consist of the salts only. Dawson Turner, in 1891, found that the electrical resistance of a normal urine amounted to about 45 ohms, and that of the blood amounted to 93·5 ohms (239). The first researches of W. Roth (240) seemed to show that the number of electrolytes is increased in cases of nephritis, and that their accumulation in the blood is, in the main, parallel to the gravity of the disease. Later experiments, on both human beings and animals, do not confirm this theory. In particular no connection with uræmia is discoverable. Even where cryoscopy showed considerable retention of extractives in the blood the electrical resistance remained, with but few exceptions [Viola (211)], within the normal limits, an indication that increased osmotic pressure is, in the main, due to storage of the non-electrolytes—*i.e.*, of the organic molecules [Richter and Roth, Bickel, Viola, Ceconi, Richter, Engelmann (241)]. This agrees with the results obtained from chemical estimations of the sodium chloride content of the blood-serum.

G.—TOXICITY OF THE SERUM; NEPHROLYSINE; INTERNAL SECRETION.

1. Toxicity of the Blood-serum.

Investigations into the urinary constituents retained in the blood of nephritic patients have produced many positive results. Now, however, it is definitely known that none of these chemical substances, such as

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urea, creatin, potassium, and other salts, etc., can be held responsible for the toxic phenomena present in cases of uræmia. This conclusion has led to an attempt to show general toxic properties in the serum of renal cases as compared with that of healthy persons. The inquiry, however, did not include an accurate determination of the chemical nature of the poison, which has yet to be ascertained. The method recommended by Bouchard for the investigation of the urine was first employed by Rummo and Bordoni (242) in testing the blood-serum. When subjected to prolonged heating at 60°, the toxicity of the serum was either destroyed or, at all events, greatly lessened. This indicated that it existed in combination with the proteid bodies of the blood. In view of recent biochemical experiments into the action of proteids introduced into the bodies of animals, this is no longer a matter for surprise. According to Strauss, the normal toxicity of human blood-serum for rabbits is between 8 and 24, usually between 10 and 20—*i.e.*, 8 to 24 c.c. of blood-serum are required to kill one animal kilogramme (203). Many such experiments have been carried out on nephritic patients both with and without uræmia, and also on cases of eclampsia. It is not easy, however, to compare the results obtained, since much depends on the technical skill of the experimenter. The conclusions have, therefore, been subjected to a keen and legitimate criticism [Albu, Herter, Ascoli (243)]. Even when all defects of method are taken into account, it seems quite certain that the toxicity of the serum in nephritis frequently exceeds the normal average (244). Uræmic and non-uræmic cases presented no differences which can be regarded as definite or characteristic. Strauss has recently emphasized the fact that sero-toxicity is, as a rule, greater in interstitial than in parenchymatous nephritis. It is useless to quote figures owing to the very great variations between the values given by the different authors.

It must here be remarked, although its biological significance is very obscure, that the blood-serum of uræmic renal patients often shows abnormal hæmolytic properties. Inactive uræmic serum, when added to active human serum, often increases its hæmolytic quality [Neisser and Döring, Laqueur, Hedinger, Wolze (245)]. According to Micheli and Senator (246), however, this is not an invariable phenomenon.

2. Nephrolysine.

Investigations of nephrotoxine have confirmed the discovery that cell-juice, when injected into the serum of animals, confers on it a specific cytolytic property over cells similar to those from which the juice has been obtained. These investigations are, certainly, full of contradictions, but they contain very interesting matter and much promise for the future.

Degeneration was caused in one kidney either by ligature of the ureter or hilum. It was expected that a substance would be taken up into the blood from the degenerating organ (autonephrotoxine), with the result that the other kidney would become impaired (247). Now and then there was slight temporary albuminuria of the healthy kidney, but no

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phenomena appeared which really suggested toxic action. Poisoning, however, was more apparent when the second kidney had been previously damaged [de Renzi (248)].

Injections of the blood-serum of animals were made into others of the same species after the former had undergone ligature of the ureter or hilum, or removal of one kidney [Néfédieff, Castaigne and Rathéry, Fiori, Anzilotti, Ascoli and Figari, Alberran and Bernard, Pearce (247)]. Some experimenters used expressed renal juice [Castaigne and Rathéry, Fiori, Pearce], or engrafted pieces of the kidney [Silvestri (250)]. By these methods it was possible to judge whether the kidneys of the injected animals were specifically injured by isonephrotoxine. Slight albuminuria occurred occasionally, just as it often does in rabbits injected with serum, but true nephrotoxic symptoms were not produced (see Pearce's careful criticism of earlier investigations).

The kidney juice of one animal was injected into others of a different species with the object of determining whether the kidneys of the injected animals suffered specifically (by heteronephrotoxine) (250). Although many experiments failed, yet it was frequently found, especially when rabbits were injected with the renal juice of dogs, that undoubted toxic, nephritic symptoms were produced. Pearce also obtained positive results when he carefully washed out the kidney with NaCl solution before compressing it. The juice obtained from the renal cortex was found to act more powerfully than the medulla.

Serum obtained from animals treated in a similar manner was injected into others of the same species in order to find whether any heteronephrotoxic substance was present. Bierry records that he obtained by this method a severe, and Pearce only a slight, impairment of the kidneys. Cafiero states that the cytotoxic sera are not strictly specific in their action; they injure other tissues beside the kidneys (252).

The serum of animals in whom renal inflammation had been produced by poisons (chromic acid) was injected into other animals of the same species, with the result that albuminuria was developed [W. Lindemann (250)]. On the other hand, it is said that the juice expressed from pigs' kidneys has caused a diminution in, or wholly cured, the albuminuria in renal patients [Renaut, Busscher (253)].

The serum of dogs suffering from spontaneous chronic renal disease was injected into other dogs. Pearce's observations showed that severe albuminuria frequently resulted. The kidneys, when examined under the microscope, showed the usual signs of inflammation. Chronic alterations in the kidneys were not produced.

Of these investigations, the latter are the most important from a clinical point of view. We cannot as yet foresee what significance they may possess in relation to the pathology and perhaps to the therapeutics of renal disease. The reader should consult Kaufmann's admirable and exhaustive summary of the literature of this subject if he would know more about this method of investigation (253A).

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3. Internal Secretion of the Kidneys.

The theories as to the internal secretion of the kidneys harmonize to some extent with what is known about nephrotoxine. The fact that dogs who have had bilateral nephrectomy performed die sooner than those whose ureters have been ligatured has been asserted by Brown-Séquard (254) and confirmed by Ascoli (255). In both cases the retention of extractives is the same, but where the kidneys have been excised there is, in addition, cessation of internal secretion. This secretion ensures the transmission to the blood of a substance which is of vital importance, just as is the case with the thyroid gland. If it is replaced by an injection of renal juice or of normal serum into animals who have undergone double nephrectomy, they live as long, or even longer, than animals who have had both ureters ligatured. After such injections normal respiration was re-established even in animals who had passed into a state of coma and Cheyne-Stokes breathing [Meyer (256)]. The inadequacy of our knowledge of the real nature of uræmia has led to the suggestion that it is shown by these results to be due to a gradual diminution of the internal secretion of the diseased kidney rather than to retention of the normal products of metabolism. This view has created considerable interest in these theories, which are certainly very attractive and suggestive (257). So far, however, very little reliable material is forthcoming, and the question has not advanced beyond the hypothetical position of Brown-Séquard. It must, however, be mentioned that in expressed renal juice (which contains the internal secretion) a substance is present which raises the blood-pressure [Meyer, Ascoli and Figari, Livon, Tigerstedt and Bergmann, Riva-Rocci (258)]. It has been stated that heteronephrotoxic serum produces the same effect, though Pearce disputes this point. The absorption of this substance, which, according to Ascoli, Riva-Rocci and Maragliano, is found in increased quantities in the diseased kidney, is said to be connected with the raised arterial tension and cardiac hypertrophy of renal patients. In spite of assiduous and careful investigation, however, we are as yet only on the threshold of this inquiry, and its future cannot be foreseen.

H.—THE PROTEIN OF THE BLOOD-SERUM.

1. Albumin and Globulin.

Researches into the relative proportions of the proteins in the blood-serum should show whether albuminuria, with its variable quantitative conditions, is brought about by pathological alterations in the mutual relations of the normal proteins, or by the appearance of new substances. This question recalls Semmola's view that nephritic albuminuria is due to "dyscrasic" alterations in the blood content rather than to perviousness of the renal filter (259). Investigations into this subject have not afforded conclusive results. The majority deal with the relation of serum-

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albumin to serum-globulin : in normal blood this equals 1·5 to 2·0 : 1. The blood of nephritic patients frequently deviates from the normal, and the records available show that the variations are always in one direction —*i.e.*, a relative increase in the globulin and a relative decrease in the serum-albumin (260). The relations rose to 2·5 and 3·0 : 1 and over. The investigations were made partly on blood-serum, partly on transudates and œdematous fluid. The increase in globulin cannot, however, be regarded as an invariable characteristic of nephritis [von Limbeck and F. Pick, J. Joachim (261)], and it is not at all clear why abnormal proportions are present in one case and not in another. In particular, the presence of globulin does not seem to bear any relation to the form and severity of the disease, although it does appear that there is an increase of this substance in almost all forms of lardaceous disease. One is much disposed to regard this condition in which the urine is rich in globulins as a possible cause of lardaceous degeneration. In other forms of renal trouble there does not seem to be any parallelism between the mutual relations of the constituents of the blood and those which prevail in the urine.

Special attention has recently been paid to the euglobulin fraction of the globulin. In two observations of Joachim it was found to constitute from 40 to 60 per cent. of the globulin (normal), whilst the urine, which was examined at the same time, contained none. I have already drawn attention to the question as to whether degeneration of the normal proteins of the blood may not be the starting-point of the non-nephritic albuminuria of adolescence.

2. Fibrin Content.

Biernacki and T. Pfeiffer have estimated the fibrin content in cases of nephritis (262, 263). No very great deviations from the normal were observed. Biernacki, however, found in a case of severe nephritis (three weeks before death) only 0·0981 per cent. of fibrin—*i.e.*, about 40 per cent. of the normal amount. He regards any considerable diminution in the quantity of fibrin as an ominous symptom. Further investigation is much needed, as at present the results obtained are but scanty. The method of Pfeiffer-Kraus is to be recommended rather than that of Biernacki. Schittenhelm and Lutter, stimulated by the important researches of Morawitz (263A), have recently found that coagulation of the blood is often considerably retarded in persons suffering from nephritis.

3. Viscosity.

Reference must here be made to researches into the viscosity of the blood, since "transpiration" of the blood [Poiseulle] is related to its protein content and to its individual protein constituents. Ewald thought that the increased internal friction of the blood might be the cause of the hypertrophy of the heart which occurs in renal disease. This question has received very careful treatment at the hands of Hirsch

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and Beck (264), and also of Bence (265). These authors have employed better methods than those formerly adopted. In twenty-one out of twenty-four renal patients the viscosity of the blood was normal; in two uræmic cases it was augmented. In eclampsia, also, it was found to be normal [Kroenig (266)]. These authors and Senator rightly concluded from these results that hypertrophy of the heart could not be accounted for by heightened viscosity of the blood (267).

4. Albumoses.

The appearance of albumoses in the plasma in interstitial nephritis is excessively rare [O. Schumm (268)]. Debove (269) states that very occasionally it is present as a milky cloudiness which falls as a fine precipitate on the addition of egg-albumin.

I.—PIGMENTS, SUGAR, FAT.

1. Serochrome.

According to Gilbert and Herascher (270) and Strauss (203), the pigmentation of the blood in cases of interstitial nephritis is either normal or above normal. The two French authors are of the opinion that the diseased kidney only excretes pigment with difficulty, and hence that the pallor of the urine in granular kidney is related to this fact. The blood-serum and œdematous fluid also are very pale in cases of parenchymatous nephritis accompanied by œdema. This probably depends on the fact that they are very dilute (hydræmia).

2. Sugar in the Blood-serum.

There has recently been a revival of interest in the older observations on the influence of atrophy of the kidney on the glycosuria of diabetes (see Diabetes), and in consequence of this many determinations have been made of the quantity of sugar present in the blood of non-diabetic renal patients. Some isolated records show that an abnormal quantity of sugar is present in the blood-serum [Lépine, Achard (271)], but many other statistics give throughout quite normal amounts both in the blood-serum, transudates, and œdematous fluid [Bock, Trinkler, Strauss, Rotmann (272)]. These figures vary from 0·05 to 0·15 per cent. My own investigations show that the normal values vary between 0·08 and 0·09 per cent. (see chapter on Diabetes).

This result was to be expected, since what is known of the CO_2 content does not suggest that there would be any increase of sugar in the blood of nephritic patients. A close investigation of the conditions will explain the apparent exceptions; Achard's patient (0·51 per cent. of sugar in the blood) had previously suffered from diabetes. Achard supposes

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that the disease made the kidneys impervious to sugar. I have myself drawn attention to an observation on a diabetic patient who died in uræmic coma (not diabetic coma). The urine contained 1·4 per cent. of sugar, and the blood at the same time 0·85 per cent. (see chapter on Diabetes).

Lævulose, as well as dextrose, has been found by Strauss (203) in the blood-serum of nephritic patients. My former assistant, M. Pickardt (272), had previously ascertained that both substances were present in cases of ascites and in pleural exudations. The significance of this discovery is as yet obscure (see Diabetes).

The fact that cases of renal disease, after injections of phloridzin, seldom develop glycosuria, or that its appearance is retarded, is in no way connected with the quantity of sugar present in the blood, but is dependent on the insufficiency of the renal epithelium. The knowledge of this fact has led to the establishment of a special method for estimating renal insufficiency. It appears to be especially reliable in comparing the functional capacity of one kidney with that of the other. I should here refer the reader interested in the question of phloridzin glycosuria to Loewi's section on the Toxicology of Metabolism.

3. Fats.

Boenniger (274) records an analysis of the fat-content of the blood; he found 1·10 per cent.—*i.e.*, a not inconsiderable increase. He gives as the normal amount 0·75 to 0·85 per cent. There is no detailed account of the nature of the illness, and the question needs further elucidation.

Neither can it as yet be decided whether an increase of fat in the blood of nephritic patients is associated with the presence of fat in the urine. Winternitz, in his researches into iodipin, found that the healthy kidney was entirely impervious to fat; in some nephritic cases some iodipin was passed into the urine, the quantity amounting to 10 per cent. of that administered by the mouth (274). This, however, hardly justifies the view of Winternitz that a corresponding fraction of the ordinary fat in the diet also passes into the urine. It is possible that the diseased and degenerate renal epithelium may possess a peculiar elective affinity for this combination of fat and iodine, and that it passes into the urine owing to the shedding of the epithelium. If this is an accurate description of what actually takes place, it can hardly be said that the diseased kidney is "pervious to fat."

VI.—URÆMIA.

It was generally supposed that poisons would be found in the blood of nephritic patients which would explain the well-known and severe symptoms of the disease. Uræmia, clinically, is only nephritis in its most advanced stage. I consider that French authors are fully justified

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when they give the name *petite urémie* to the symptoms which usually accompany renal disease, such as increased blood-pressure, cardiac hypertrophy, headache, digestive troubles, etc., instead of reserving the word for a condition characterized by unconsciousness and convulsions. What are these poisons? In the section on the Chemistry of the Blood mention was made of the fact that for the last fifty years almost all those normal products of metabolism not easily excreted by the diseased kidney have been held responsible for uræmic intoxication. It is not probable, however, that special importance can be assigned to any one of them. On the contrary, it is now known definitely that for many such a theory cannot hold good—urea, for instance. The theories which regard ammonia, creatin, uric acid, diminution of alkalis, potassium salts, chlorides, increased osmotic pressure, etc., as possible causes of uræmia have been already referred to. Not one of these can stand the test of close investigation.

Even the total toxic effect produced by all known urinary substances does not fully account for uræmic poisoning. Ascoli has established this in his very thorough critical inquiry (3). It cannot, however, be affirmed that these negative results entirely exclude the possibility that poisoning may be directly caused by the retention of urinary substances. The available methods for estimating the degree of toxicity produced are very rough and inadequate. The greatest objection to them is that they only induce acute toxic effects, whereas the very shortest period of poisoning in nephritis extends over several days, and usually over months and years. The clinician and the laboratory worker are well aware how very different are the features presented by acute and chronic poisons, as, indeed, is evidenced by plumbism.

Also, it is perhaps not in the blood itself that these toxines should be looked for. It has already been frequently pointed out that the tissues themselves can absorb a large quantity of extractives. Certain cells have a special affinity for certain substances—*e.g.*, some nerve cells attract morphia, others the toxine of tetanus. We search in vain for these substances in the blood, even at a time when they are present in fatal amounts, in cells of vital importance. This is true of ammonia, as was stated in the section on the Extractives of Metabolism. A thorough inquiry into the localization of these extractives, and their toxic action in cases of renal incapacity, is much needed. So far the question has hardly been approached. The results of such an inquiry may show that the deposition and chemical combination of extractives in the cells (especially in the nervous system)—in the very place, that is, where they exercise their toxic effect—are associated with a previous definite condition of such cells, and that this condition, as well as the degree of retention, is a factor to be taken into account. It will also be necessary to ascertain how, and to what extent, glands such as the thyroid and suprarenal glands, etc., react to the intoxication, whether by insufficient or excessive secretion, or by the production of poisons, or by the neutralization of the products of metabolism. When we are acquainted with all the factors which probably go to determine the appearance, progress, and prevention of uræmia, it will no longer seem strange that it cannot be

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correctly estimated or adequately explained either by the deficit in the metabolic balance or by quantitative analyses of the blood.

Notwithstanding all this, however, it does not seem to me permissible to entirely put on one side the theory that uræmia is associated with poisoning by extractives, and to assign to the disease an entirely new origin. In this matter I consider that Ascoli goes much too far. There are certainly many indications that new knowledge will lead to the modification and completion of the older view. New vistas are opened out, both by the theory of the internal secretion of the kidneys (although as yet the evidence for this is scanty) and also by the interesting inquiries into nephrolysine. Their value from the heuristic standpoint is undoubted, and they should prove a stimulus to further investigation. At the same time, we are not as yet in a position to formulate a fresh theory of nephritic and uræmic intoxication on such a basis.

VII.—THE GENESIS OF ŒDEMA.

Current theories concerning nephritic œdema have suffered much from the adoption of too one-sided an attitude. Mistakes have frequently resulted from an attempt to give a too uniform explanation of its development, whilst theories which would undoubtedly hold good under many conditions have been put altogether on one side, simply because they were not applicable to certain cases. This is what has happened, for instance, in regard to the old hypothesis, based upon simple clinical observation, that in nephritis the excretion of water is insufficient, and hence that it accumulates in the blood and tissues, together with other urinary substances, thus causing hydræmia and dropsy of the skin and serous cavities. No one disputes the justice of this simple position in cases of heart disease. Doubt, however, has been thrown on its applicability to nephritis, or it has only been admitted in those cases of interstitial nephritis in which, towards the end of life, cardiac failure rather than renal incapacity is the dominant feature of the illness. The well-known experiments of Cohnheim and Lichtheim, whose main positions have received frequent corroboration, are adduced as evidence of the inadequacy of the theory, as well as the fact that patients with non-nephritic acute anuria, even when it persists for several days, do not develop œdema (275). The value of these experiments on animals for human pathology has rightly been disputed. The antithesis between acute experimental hydræmia and plethora, as investigated by these two authors, and the condition observed in man, is, however, not so essential as at first appeared. Pathological, extravascular dropsy was also found by Cohnheim and Lichtheim; it was only the anasarca that was absent. This proves that, in investigations carried out on healthy animals, channels other than those used by human beings were selected for the excretion of the superfluous water, and especially that the skin of animals is more resistant to transudation than is the human skin.

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Richter has recently succeeded, by means of uranium salts, in producing nephritic anasarca in nine animals. This is the first success of experimental pathology in this direction. It was quite apparent from these experiments that the amount of the œdema and transudate was determined by the water intake. NaCl also produced œdema in animals poisoned with uranium salts, but only in those instances in which water was taken copiously.

The opponents of the theory of the mechanical accumulation of water are quite mistaken when they refer for support to cases of acute non-nephritic anuria or to acute sublimate nephritis. Œdema is not developed by these patients, for they take or retain so very little food, either liquid or solid, that superfluous water cannot accumulate in the blood and tissues. If, however, large quantities of milk and mineral waters are given to an oliguric, nephritic patient in order to "wash out the kidneys," a very different result ensues. It is known that evaporation of water through the lungs is almost constant in amount, and depends more on external than on bodily conditions (dampness of the air); also that there is certainly no increase of perspiration in nephritis, and that it is only in exceptional cases that water is excreted via the intestines. It is, therefore, necessary to fall back on the theory that disturbances of the water balance in this disease are purely mechanical in origin, just as they are in cases of heart disease and in the animals treated by Richter with uranium salts. There are, of course, other factors to be taken into account, but to refuse to admit the important part played by the simple relation between the intake of water and the capacity for its excretion in all cases of nephritic thirst is not to see the wood for the trees. I have often pointed out the significance of this fact from a therapeutic point of view (also in acute glomerulo-nephritis) [von Noorden, P. F. Richter (275B)].

In many respects, however, renal œdema differs from cardiac dropsy. In the first place, the composition of the blood is not the same. In nephritis the blood is much more hydræmic. It was this fact that led at one time to the suggestion that hydræmia was the cause of nephritic œdema. In this general form, however, the theory cannot be maintained. In the first place, nephritic œdema may be present without pronounced hydræmia [von Jaksch, W. Bruner (276)], and in the typical cases of acute nephritis already mentioned severe hydræmia never appears before the œdema [Senator (277)]. Further, hydræmia may be present without œdema [Benczur and Czatáry, Ochremowsky (278)]—*e.g.*, a hydræmic condition of the blood may persist for a long time in cases of parenchymatous nephritis in which the patients have long been free from œdema and the disease has passed on into a secondary stage of cirrhosis. Also, although when hydræmia and œdema exist side by side their variations are, as a rule, in the same direction, yet there is no certainty that they will be equal in amount. After making full allowance for these objections, however, it cannot be denied that a certain, though perhaps a slight, degree of hydræmia must be present before water can accumulate in the tissues. This may occur quite temporarily, and perhaps only after an intake of water and its absorption from the in-

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testine. In these cases of acute and chronic parenchymatous nephritis the action of the kidney is too slow (according to the so-called "dilution experiment"). The osmotic pressure of the blood has to be maintained, and the superfluous water is, therefore, transferred to the tissues. The phenomena of cardiac dropsy may be exactly the same, and there is no reason to suppose that the same factor does not operate, together with others, in renal dropsy. This would account for the fact that, although œdema may be present when acute nephritis is first set up, no hydræmia is found. As the disease progresses the blood also suffers from the excessive supply of water coming from both the intestinal canal and the tissues, and from its incomplete excretion by the kidneys. Hydræmia supervenes. When this stage has been reached, as in the case of dropsical heart disease, loss of protein must be held accountable for some of the symptoms. Hydræmia is always associated with hypalbuminæmia. This was first demonstrated with absolute certainty by von Jaksch (188). The existence of definite relations between loss of protein and hydræmia was also established by Dieballa and von Kétly (188), after examination of a large amount of material, subjected to a uniform method of investigation. Renal cases, however, are usually given a diet poor in protein for a much longer period than are heart cases, and it has not been ascertained whether such a treatment may not exert an injurious influence on the concentration of the plasma [Grawitz (194)], quite independently of other complications, which may impair the constitution of the blood.

I have discussed the available instances of quantitative estimation in some detail, because it appears to me that the simple theory of the accumulation of water through renal incapacity has been too much neglected in favour of other increasingly popular theories as to the origin of nephritic œdema. Although I may assign to mere accumulation of water a certain, and in many cases the most important, share in the production of œdema, I fully recognise that it does not explain all the strange phenomena presented by renal dropsy. Relying on Cohnheim's investigations (279), I have already emphasized the fact that many forms of renal dropsy cannot be accounted for by the disparity between the intake of water and its excretion in the urine (280). In some stages of the disease water was attracted to the blood and tissues, with the result that little was excreted. The rapid development of dropsy in glomerulo-nephritis, and the mutual relations of dropsy and diuresis in the more protracted forms of acute nephritis and in chronic parenchymatous Bright's disease, also support this view. Diuresis in these cases is often excellent. It can be increased by a liquid diet, and the impression is certainly conveyed that water passes out through the kidneys, although its transmission may be somewhat retarded. Notwithstanding this, however, the œdema remains stationary for weeks and months together, and recurs even after any temporary subsidence due to excessive diaphoresis. Numerous clinical observations have shown that it persists even in spite of a considerable diminution in the supply of water. There is much that suggests that in these cases toxic substances are retained or formed in the body which increase the attractive capacity of the blood, and especially of the tissues, for water [von Noorden (280)].

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This hypothesis has received strong support from an extension of the investigations of Cohnheim and Lichtheim. It has been shown that the presence of certain poisons in the blood favours the development of anasarca. They make the walls of the capillaries more pervious [Magnus, Grosz and Reichel, Senator (281)], or, as Johnson (282) puts it, stimulate them to " active secretion." An analogous phenomenon is presented by the toxic œdema mentioned by Magnus as occurring occasionally after morphia, and frequently after iodide of potassium. We are not yet acquainted with all the more subtle phenomena which accompany toxic œdema. It is enough to know that they exist, for there is every reason to suppose that there is in nephritis also a direct toxic action on the capillaries. Inquiries into the action of lymphagogic substances also suggest the correctness of this view. The investigations of Heidenhain, Grawitz (283), and others, have shown that a whole series of substances exist which exert a powerful influence on the exchange of fluids between the blood and the tissues. Hamburger (284) and von Noorden (280) have already suggested tentatively that these bodies may contribute towards the development of nephritic œdema. As a matter of fact, the work of Starling (285) and of Kast (286) tend to show that lymphagogic bodies are present in the blood-serum of renal patients.

These suggestions, however, do not appear to exhaust the train of causes which may lead to œdema in nephritis ; for, thanks to the careful work of certain French authors, it has been shown that the accumulation of NaCl in the body may bring about retention of water in the tissues, owing to its effect on the osmotic pressure [Claude et Manté, Widal, Widal and Lemierre, Widal and Javal, Castaigne and Rathéry]. A similar view has already been expressed by Lazarus-Barlow (287). This author, however, holds that the tendency of the tissues to attract water is due rather to the organic products of disintegration, and their influence on the osmotic pressure, than to the presence of sodium chloride. Magnus has already emphasized the fact, for both physical and chemical reasons, that this theory is a very improbable one.

Thus we must come to the conclusion that, so far, the problem of œdema has not been satisfactorily solved. It seems to me, however, that much has already been gained if the view that it is invariably due to a uniform cause is abandoned. Further inquiry would be rendered fruitless if any explanation by which some of the phenomena could be fully accounted for were thrown aside *a priori* simply because it did not hold good for other cases. I recall, for instance, the theory as to the dependence of œdema upon the retention of chlorides. After Widal's excellent observations on œdematous patients, I do not think anyone can doubt that the cause of the disease in his cases was the imperviousness of the kidney to chlorides, and its retention in the fluids of the body. The same thing is true of the other cases previously mentioned. It would be very perverse to deny this. On the other hand, we should be greatly wanting in critical acumen were we to suppose that this is the only, or even the most important, etiological factor in the production of the condition, and in consequence to regulate the entire diet of renal patients on " osmotic principles."

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VIII.—VICARIOUS SECRETION OF URINARY CONSTITUENTS BY OTHER PARTS OF THE BODY.

The recognition of the inadequate elimination of the waste products in renal disease soon led to the supposition that they are excreted vicariously by other parts of the body. A more accurate knowledge of these processes is of practical as well as of theoretical importance, for it is possible that nature might be assisted by artificial stimulation of such vicarious functions.

1. Urea.

Investigations into this subject relate, for the most part, to urea, and show that its presence in the secretions of the various forms of nephritis, and especially in uræmia, is easily demonstrated even in those cases in which traces only occur. This is primarily true of the saliva and perspiration, to a slighter degree of the gastric juice, and probably also of the milk, which, even in health, contains traces of urea.

It is not clear, however, whether these additions to the substances ordinarily excreted by the skin and mucous membrane really constitute a true vicarious secretion. Such an expression is only permissible when, as a result of disease, a capacity to attract urea similar to that of the healthy kidney is developed by those glands which ordinarily only take up traces of urea from the blood. It is a mistake to speak of " vicarious secretion " in cases where a certain amount of urea is found in glandular secretions owing to the fact that the blood is heavily laden with the substance. This is the case in renal diseases. The saliva and sweat, even where the retention of urea is great, contain so small an amount of the substance that one can hardly speak of a true elective secretion. (Consult also Urea in the Saliva, Gastric Juice, and Intestinal Secretions.)

The elimination of urea in the perspiration is greater than in the saliva, because in the former case it is not taken up again into the circulation. As a rule, there is no question of the elimination of urea by sudoriparous glands in nephritis, because—a fact long known—these patients hardly perspire at all. There is even a tendency to diminution of the insensible perspiration (*perspiratio insensibilis*), both in œdematous [Pollacci (289)] and in non-œdematous patients [Schwenkenbecher (290)]. If perspiration is artificially induced, nitrogen and, what is more significant, urea are found. The nitrogen content of normal perspiration is said to vary from 0·5 to 1 per cent. [Leube, Argutinsky, Cramer, Harnack, Köhler, Strauss, Camerer junr., Easterbrook (291)]. The method employed to make the patient perspire obviously affects the results [Brieger and Diesselhorst (292)]. An examination of the perspiration taken from different parts of the body shows variations in the amount of urea. For instance, in a case of rheumatism, I found, after administration of pilocarpin, that the perspiration of the forehead contained 0·8 per cent. of nitrogen, whilst that of the abdomen contained 0·31 per cent. Where violent sweating is induced the absolute quantity of nitrogen which may

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be thus spared from excretion in the urine is estimated at 0·3 to 1 gramme daily [Argutinsky]. Some isolated records show even higher values [Cramer, Eijkman (293)].

It was hoped that by inducing perspiration it would be quite easy to diminish the increased quantities of urinary substances which are present in the blood of nephritic patients. Unfortunately, however, this hope has not been fulfilled [von Leube (294)]. In connection with the investigations carried out by Ritter (295) and myself, I gave the amount of nitrogen usually found in any one sample of the skin perspiration of a nephritic patient as not more than 0·5 gramme. This still seems to hold good in the main, although it sometimes happens that a much higher value is reached (296). Köhler's experiments frequently show a loss of nitrogen through the perspiration amounting to from 1 to 1·6 grammes, but on other days much smaller amounts were found in the same patients. My own observations confirm this striking variation in the loss of nitrogen. I append the results of two series of observations carried out in the summer of 1893, the subjects being young women with parenchymatous nephritis and very marked retention of nitrogen. Unfortunately, I have lost the records of the exact nitrogen balances.

Total nitrogen loss through the perspiration (after pilocarpin) :

Day.	*First Patient.*	*Second Patient.*
	Gm. Nitrogen.	Gm. Nitrogen.
1	1·20	0·68
2	0·49	0·92
3	0·59	0·51
4	0·87	0·93

The amount here given (1·2 grammes nitrogen output during perspiration) is the largest I have ever found amongst the numerous investigations I have made upon nephritic cases (summer, 1893). Köhler, Roth-Schulz and Kövesi (296) state that, in one perspiration, a loss of 2 grammes nitrogen and an equal amount of NaCl is not infrequent. Personally, I consider that any value which considerably exceeds 1 gramme nitrogen is exceptional. Also, I cannot help questioning whether, as Roth-Schulz and Kövesi maintain, a concentration of 0·4 per cent. of nitrogen and over can really be shown to exist in a copious flow of perspiration artificially induced. My own experience would rather lead me to suppose that some mistakes have arisen owing to the complex nature of the experiments. Such values are certainly not too high for cases of uræmia and of cholera, where the perspiration exudes slowly; but in these a certain quantity of the water evaporates during the secretion, and the sweat is consequently more concentrated.

Profuse sweating may cause a slight and temporary increase of the osmotic pressure of the blood in healthy persons, but in cases of dropsical nephritis it either remains unchanged or is somewhat lowered [Bendix, Roth-Schulz, and Kövesi (297)]. We cannot, however, conclude from

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this that substances relatively more constant constituents than water are removed from the blood. The explanation seems rather to be that the loss of water is more than compensated for by the addition to the blood of water from the tissues.

During a period of perspiration extending over five days von Noorden and Ritter found just as much nitrogen in the urine of their patients as they had obtained prior to the experiment. The nitrogen of the sweat was additional. Kövesi and Roth-Schulz observed the same thing. If a healthy person perspires freely, the amount of urea in the urine is diminished [Leube, Dapper (298)]. This is obviously the result of the elimination of nitrogen in the perspiration. Thus it is not possible to diminish the quantity of nitrogen in a healthy person by inducing perspiration, because the nitrogen of the sweat compensates for its deficiency in the urine. In a woman suffering from renal disease, however, this was successfully done. Unfortunately, such a result does not always obtain, for Köhler frequently found in the renal cases he had under observation that the nitrogen of the urine was diminished when the substance was drawn off through the skin. If we bear this fact in mind, and recall the enormous quantity of nitrogenous products of disintegration which often accumulate in renal disease, we shall no longer exaggerate the importance of the skin as a substitute for the kidneys in this respect.

Uræmic patients seem to excrete larger amounts of urea through the skin than has ever been observed in non-uræmic cases. This was first found to be the case in the nephritis of cholera. Crystals of urea were present on the skin. The same thing has been observed in the uræmic stage of interstitial nephritis (299). At the same time, I must say that my own experience shows the condition to be a very exceptional one. It is possible that, where there is acute poisoning, the functions of the sweat-glands become qualitatively altered, and that this may be a true instance of " vicarious secretion." It is not advisable, however, to bring about elimination of urea in patients suspected of uræmia by stimulation of the sweat-glands, for, although in many cases no harm is done, yet in others the onset of the perspiration coincides so precisely with a uræmic convulsion that we can only conclude that they are causally connected. Walko (300), and before him Leube, have drawn attention to the fact that sweating promotes the excretion of water to a much greater degree than that of solid substances, and that this loss of water may result in a rapid and dangerous concentration of poisonous matters. This warning is undoubtedly justifiable, and will be carefully borne in mind by every experienced practitioner. According to cryoscopical investigations, the concentration of the blood is a matter of less importance than that of the tissue fluids.

2. Uric Acid.

Uric acid is a normal constituent of the sweat, although it is only present in very small quantities [Tichborne, Camerer junr., Bottazzi (301)]. I have not found any reliable records as to its special behaviour in renal disease. In some investigations upon sweat commenced in the summer

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of 1893, but not yet completed, I was able, by means of the murexide test, to demonstrate in three instances the presence of uric acid in cases of renal disease (evaporation of the sweat after the addition of hydrochloric acid until the sodium chloride was just kept in solution; the precipitate was collected, dissolved in dilute sodium hydrate solution, and then treated according to the Ludwig-Salkowski method). Even on examination of 250 c.c. of sweat the substance was never present in sufficient amount to permit of a quantitative estimation being made. In two cases the murexide reaction failed, although there was an increase of uric acid in the blood. These patients only perspired slightly, and the sweat retained an acid reaction, whilst in the three cases where the result was positive there was profuse perspiration with neutral or only slight reaction. It appears from this that the elimination of uric acid was connected with the reaction of the secretion. So far, however, the number of experiments carried out is insufficient to establish this as a general rule. We can hardly maintain that there is any diminution of uric acid in the body owing to its secretion in the sweat.

3. Ammonia.

Ammonia salts are found on the free surfaces of the skin and mucous membrane in severe renal disease, and especially in its uræmic stages. Frerichs based on this fact his well-known theory that a ferment in the blood transforms accumulated urea into ammonium carbonate, and that this substance, by exerting a toxic action, produces uræmia. This theory, however, has now been abandoned. It has also been thought that the ammonia present on the skin and mucous membrane was probably formed on the spot from other nitrogenous substances (especially from urea) by the agency of bacteria. This, again, has been disputed, since it has been shown that the presence of ammonia combinations in glandular secretions is normal [in the gastric juice, Rosenheim, Strauss, Thomson, and others; in the sweat, Camerer (302)]. Since there is a certain increase in the ammonia of the blood in uræmia, there is nothing to be said against the view that the higher values present in the saliva [Thiry, Kühne, Schottin (303)], the stomach and intestines [Treitz, von Jaksch, Brauneck, Leo, Martins and Lüttke (304)] of nephritic patients are to be attributed to an increase of the secretions. This would account for the local production of ammonia from urea. This is more particularly true of the large intestine. Brauneck found in the fæces of a nephritic patient as much as ten times the normal quantity of ammonia (0·343 per cent., as against 0·641 per cent.). Thus it appears to me that ammonia is associated with the increase of nitrogen in the fæces of nephritis, and often to a much greater extent than has hitherto been supposed; for in the profuse diarrhœa of uræmic intestinal ulceration and lardaceous disease it is easy to discover free ammonia after the fæces have become alkaline in reaction. It is well known that the corrosive action of the ammonia combinations formed from urea is the cause of ulceration in uræmia.

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Since it is not definitely known how much of the ammonia found on the surface of the skin and mucous membranes is due to its actual secretion from the blood, it is impossible to determine how far this secretion may be regarded as vicarious.

4. Excretion of Toxines.

There is a widespread conviction that the sweat contains toxines, and serves as an important vehicle for their elimination. This supposition plays an important part in popular medical literature, and in the so-called nature cures. As a matter of fact, the results of scientific inquiry militate entirely against such a view [Arloing, Mavrojannis, Cabitto, Mairet and Ardin-Delteil, Cofiero, and others (305)]. The degree of poisoning has been determined by intravenous or subarachnoidal injection of rabbits. This method is open to some objection, and the results are often contradictory [Capitan and Gley (306)]. In particular, sufficient consideration has not been given to the fact that the molecular concentration of the perspiration is very slight [Strauss, Brieger and Diesselhorst (292)], and consequently that the blood and tissues are damaged for purely physical reasons. There are no really serviceable estimations of the elimination of poisons in the perspiration of renal cases, and still fewer concerning the nature of these poisons. It is important that these matters should receive further investigation.

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